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(54) **Processes for the diastereo-selective synthesis of nucleosides**

Verfahren zur diastereoselektiven Synthese von Nukleosiden

Procédé pour la synthèse diastéréosélective de nucléosides

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(56) References cited:

EP-A- 0 071 926 EP-A- 0 266 042
EP-A- 0 322 384 EP-A- 0 337 713
EP-A- 0 382 526 WO-A-91/17159
FR-A- 1 445 013

- SYNTHESIS. no. 11, November 1991, STUTTGART DE pages 1046 - 1048; J.-L. KRAUS ET AL.: 'Synthesis of New 2,5-Substituted 1,3-Oxathiolanes. Intermediates in Nucleoside Chemistry.'
- JOURNAL OF ORGANIC CHEMISTRY. vol. 46, 1981, EASTON US pages 3353 - 3354; E.VEDEJS ET AL.: 'Method for Sulfide S-Benzoylation or S-Allylation Using Trimethylsilyl Triflate Activated Benzyl or Allyl Ethers'
- JOURNAL OF ORGANIC CHEMISTRY. vol. 54, no. 9, 1989, EASTON US pages 2217 - 2225; C.K.CHU ET AL.: 'General Synthesis of 2',3'-Dideoxynucleosides and 2',3'-Didehydro-2',3'-Dideoxynucleosides'
- TETRAHEDRON LETTERS. vol. 31, no. 13, 1990, OXFORD GB pages 1815 - 1818; L.J.WILSON ET AL.: 'A General Method for Controlling Glycosylation Stereochemistry in the Synthesis of 2'-Deoxyribose Nucleosides'

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EP 0 515 156 B1

Description

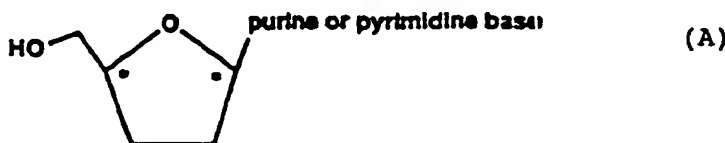
FIELD OF THE INVENTION

The present invention relates to diastereoselective processes for preparing optically active *cis*-nucleosides and nucleoside analogues and derivatives. The novel processes of this invention allow the stereo-controlled synthesis of a given enantiomer of a desired *cis*-nucleoside or nucleoside analogue or derivative in high optical purity. This invention also relates to novel intermediates useful in the processes of this invention.

BACKGROUND OF THE INVENTION

Nucleosides and their analogues and derivatives are an important class of therapeutic agents. For example, a number of nucleosides have shown antiviral activity against retroviruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and human T-lymphotropic virus (HTLV) (PCT publication WO 89/04662, and European Patent publication 0349242 A2). Among the nucleosides shown to have antiviral activity are 3'-azido-3'-deoxythymidine (AZT) and 2',3'-dideoxycytidine (DDC).

Most nucleosides and nucleoside analogues and derivatives contain at least two chiral centers (shown as * in formula (A)), and exist in the form of two pairs of optical isomers (i.e., two in the *cis*-configuration and two in the *trans*-configuration). However, generally only the *cis*-isomers exhibit useful biological activity.



Different enantiomeric forms of the same *cis*-nucleoside may, however, have very different antiviral activities. M.M. Mansuri et al., "Preparation Of The Geometric Isomers Of DDC, DDA, D4C and D4T As Potential Anti-HIV Agents", *Bioorg.Med.Chem. Lett.*, 1 (1), pp. 65-68 (1991). Therefore, a general and economically attractive stereoselective synthesis of the enantiomers of the biologically active *cis*-nucleosides is an important goal.

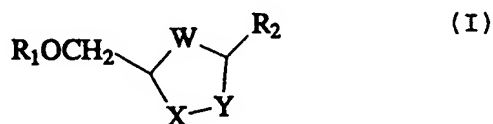
It is known that racemic mixtures can be separated using chiral auxiliaries (see, e.g., EP-A-226042). EP-A-071926 discloses the preparation a 4'-carboxyadenosine derivative in racemic form.

Many of the known processes for producing optically active nucleosides and their analogues and derivatives modify naturally occurring (i.e., optically active) nucleosides by altering the base or by altering the sugar via reductive procedures such as deoxygenation or radical initiated reductions. C.K. Chu et al., "General Synthesis Of 2',3'-Dideoxynucleosides And 2',3'-Didehydro-2',3'-Dideoxynucleosides," *J.Org.Chem.*, 54, pp. 2217-2225 (1989). These transformations involve multiple steps, including protection and deprotection and usually result in low yields. Moreover, they begin with and maintain the optical activity of the starting nucleoside. Thus, the nucleosides produced by these processes are limited to specific analogues of the enantiomeric form of the naturally occurring nucleoside. In addition, these procedures require the availability of the naturally occurring nucleoside, often an expensive starting material.

Other known processes for producing optically active nucleosides rely on conventional glycosylation procedures to add the sugar to the base. These procedures invariably give anomeric mixtures of *cis*- and *trans*-isomers which require tedious separation and result in lower yields of the desired biologically active *cis*-nucleoside. Improved glycosylation methods designed to yield only the *cis*-nucleoside require addition of a 2'- or 3'-substituent to the sugar. Because the 2'- or 3'-substituent is only useful in controlling *cis*-nucleoside synthesis in one configuration (when the 2' or 3' substituent is *trans*-to the 4' substituent), multiple steps are required to introduce this substituent in the proper configuration. The 2'- or 3'-substituent must then be removed after glycosylation, requiring additional steps. L. Wilson and D. Liotta, "A General Method For Controlling Stereochemistry In The Synthesis Of 2'-Deoxyribose Nucleosides", *Tetrahedron Lett.*, 31, pp. 1815-1818 (1990). Furthermore, to obtain an optically pure nucleoside product, the starting sugar must be optically pure. This also requires a series of time-consuming syntheses and purification steps.

SUMMARY OF THE INVENTION

The present invention overcomes the difficulties and shortcomings of the prior art and provides processes for producing optically active *cis*-nucleotides and nucleoside analogues and derivatives of formula (I)



wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

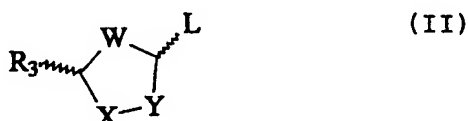
Z is hydrogen, hydroxyl, alkyl or acyl;

R₁ is hydrogen or acyl; and

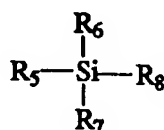
R₂ is a purine or pyrimidine base or an analogue or derivative thereof;

provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂; and further provided that when X is CH then Y is also CH.

The processes of this invention comprise the step of glycosylating a desired purine or pyrimidine base or analogue or derivative thereof with a single enantiomer of the compound of formula (II)



wherein R₃ is a substituted carbonyl or carbonyl derivative and L is a leaving group. Glycosylation is accomplished using a Lewis acid of the formula (III)



wherein R₅, R₆, R₇, and R₈ are defined below and the resulting intermediate is reduced to give a nucleoside or nucleoside analogue or derivative of formula (I).

The processes of this invention have the advantages of allowing preparation of a nucleoside of formula (I) (or analogues or derivatives thereof) without using expensive starting materials, cumbersome protection and deprotection steps or addition and removal of 2'- or 3'-substituents. The processes of this invention produce nucleosides in high yields, with high purity and high optical specificity. The processes of this invention have the further advantage of generating nucleosides whose stereoisomeric configuration can be easily controlled simply by the selection of the appropriate starting materials.

DETAILED DESCRIPTION OF THE INVENTION

In the processes for preparing optically active compounds of this invention in a configurational- and diastereo-selective manner, the following definitions are used:

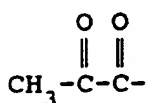
R₂ is a purine or pyrimidine base or an analogue or derivative thereof.

A purine or pyrimidine base is a purine or pyrimidine base found in naturally occurring nucleosides. An analogue thereof is a base which mimics such naturally occurring bases in that their structures (the kinds of atoms and their arrangement) are similar to the naturally occurring bases but may either possess additional or lack certain of the func-

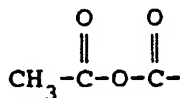
tional properties of the naturally occurring bases. Such analogues include those derived by replacement of a CH moiety by a nitrogen atom, e.g., 5-azapyrimidines such as 5-azacytosine) or vice versa (e.g., 7-deazapurines, such as 7-deazaadenine or 7-deazaguanine) or both (e.g., 7-deaza, 8-azapurines). By derivatives of such bases or analogues are meant those bases wherein ring substituents are either incorporated, removed, or modified by conventional substituents known in the art, e.g., halogen, hydroxyl, amino, C₁₋₆ alkyl. Such purine or pyrimidine bases, analogues and derivatives are well known to those skilled in the art.

A "nucleoside analogue or derivative" is a nucleoside which has been modified in any of the following or combinations of the following ways: base modifications, such as addition of a substituent (e.g., 5-fluorocytosine) or replacement of one group by an isosteric group (e.g., 7-deazaadenine); sugar modifications, such as substitution of the C-2 and C-3 hydroxyl groups by any substituent, including hydrogen (e.g., 2',3'-dideoxynucleosides), replacement of any ring CH group or the ring oxygen with a heteroatom; alteration of the site of attachment of the sugar to the base (e.g., pyrimidine bases usually attached to the sugar at the N-1 site may be, for example, attached at the N-3 or C-6 site and purines usually attached at the N-9 site may be, for example, attached at N-7); alteration of the site of attachment of the base to the sugar (e.g., the base may be attached to the sugar at C-2, such as iso-DDA); or alteration of configuration of the sugar-base linkage (e.g., cis or trans configurations).

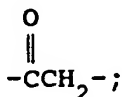
R₃ is a carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkylsiloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol; C₆₋₂₀ aryl; C₁₋₂₀ alkenyl; C₁₋₂₀ alkynyl; 1,2-dicarbonyl, such as



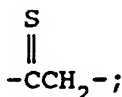
substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydrides such as



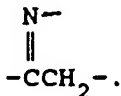
substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; a homologue of carbonyl, e.g.,



a homologue of thiocarbonyl, e.g.,



or a homologue of azomethine, such as



The preferred substituted carbonyl/carbonyl derivatives are alkoxy-carbonyls, such as methyl, ethyl, isopropyl, t-butyl and menthyl; carboxyls; diethyl-carboxamide; pyrrolidine amide; methyl ketone and phenyl ketone. The more preferred substituted carbonyl/carbonyl derivatives are esters and carboxyls and the most preferred are esters.

R₄ is a chiral auxiliary. The term "chiral auxiliary" describes asymmetric molecules that are used to effect the chemical resolution of a racemic mixture. Such chiral auxiliaries may possess one chiral center such as methylbenzylamine or several chiral centers such as menthol. The purpose of the chiral auxiliary, once built into the starting material, is to allow simple separation of the resulting diastereomeric mixture. See, for example, J. Jacques et al., Enantiomers, Racemates

5 And Resolutions, pp. 251-369, John Wiley & Sons, New York (1981).

R₅, R₆ and R₇ are independently selected from the group consisting of hydrogen, C₁₋₂₀ alkyl (e.g., methyl, ethyl, t-butyl), optionally substituted by halogens (F, Cl, Br, I), C₁₋₆ alkoxy (e.g., methoxy) or C₆₋₂₀ aryloxy (e.g., phenoxy); C₇₋₂₀ aralkyl (e.g., benzyl), optionally substituted by halogen, C₁₋₂₀ alkyl or C₁₋₂₀ alkoxy (e.g., p-methoxybenzyl); C₆₋₂₀ aryl (e.g., phenyl), optionally substituted by halogens, C₁₋₂₀ alkyl or C₁₋₂₀ alkoxy; trialkylsilyl; halogens (F, Cl, Br, I).

10 R₈ is selected from the group consisting of halogen (F, Cl, Br, I); C₁₋₂₀ sulphonate esters, optionally substituted by halogens (e.g., trifluoromethane sulphonate); C₁₋₂₀ alkyl esters, optionally substituted by halogen (e.g., trifluoroacetate); polyvalent halides (e.g., triiodide); trisubstituted silyl groups of the general formula (R₅)(R₆)(R₇)Si (wherein R₅, R₆, and R₇ are as defined above); saturated or unsaturated selenenyl C₆₋₂₀ aryl; substituted or unsubstituted C₆₋₂₀ arylsulfenyl; substituted or unsubstituted C₁₋₂₀ alkoxyalkyl; and trialkylsiloxy.

15 L is a "leaving group", i.e., an atom or a group which is displaceable upon reaction with an appropriate purine or pyrimidine base, with or without the presence of a Lewis acid. Suitable leaving groups include acyloxy groups, alkoxy groups, e.g., alkoxy carbonyl groups such as ethoxy carbonyl; halogens such as iodine, bromine, chlorine, or fluorine; amido; azido; isocyanato; substituted or unsubstituted, saturated or unsaturated thiolates, such as thiomethyl or thiophenyl; substituted or unsubstituted, saturated or unsaturated seleno, seleninyl, or selenonyl compounds, such as phenyl selenide or alkyl selenide.

20 A suitable leaving group may also be -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl group, e.g., C₁₋₆ alkyl or alkenyl group; a substituted or unsubstituted aliphatic or aromatic acyl group, e.g., a C₁₋₆ aliphatic acyl group such as acetyl and a substituted or unsubstituted aromatic acyl group such as benzoyl; a substituted or unsubstituted, saturated or unsaturated alkoxy or aryloxy carbonyl group, such as methyl carbonate and phenyl carbonate; substituted or unsubstituted sulphonyl imidazolidine; substituted or unsubstituted aliphatic or aromatic amino carbonyl group, such as phenyl carbamate; substituted or unsubstituted alkyl imidate group such as trichloroacetamidate; substituted or unsubstituted, saturated or unsaturated phosphonate, such as diethylphosphonate; substituted or unsubstituted aliphatic or aromatic sulphinyl or sulphonyl group, such as tosylate; or hydrogen.

30 As used in this application, the term "alkyl" represents a substituted (by a halogen, hydroxyl or C₆₋₂₀ aryl) or unsubstituted straight chain, branched chain, or cyclic hydrocarbon moiety having 1 to 30 carbon atoms and preferably, from 1 to 6 carbon atoms.

The terms "alkenyl" and "alkynyl" represent substituted (by a halogen, hydroxyl or C₆₋₂₀ aryl) or unsubstituted straight, branched or cyclic hydrocarbon chains having 1 to 20 carbon atoms and preferably from 1 to 5 carbon atoms and containing at least one unsaturated group (e.g., allyl).

35 The term "alkoxy" represents a substituted or unsubstituted alkyl group containing from 1 to 30 carbon atoms and preferably from 1 to 6 carbon atoms, wherein the alkyl group is covalently bonded to an adjacent element through an oxygen atom (e.g., methoxy and ethoxy).

The term "amine" represents alkyl, aryl, alkenyl, alkynyl, or aralkyl groups containing from 1 to 30 carbon atoms and preferably 1 to 12 carbon atoms, covalently bonded to an adjacent element through a nitrogen atom (e.g., pyrrolidine).

40 They include primary, secondary and tertiary amines and quaternary ammonium salts.

The term "thiol" represents alkyl, aryl, aralkyl, alkenyl or alkynyl groups containing from 1 to 30 carbon atoms and preferably from 1 to 6 carbon atoms, covalently bonded to an adjacent element through a sulfur atom (e.g., thiomethyl).

45 The term "aryl" represents a carbocyclic moiety which may be substituted by at least one heteroatom (e.g., N, O, or S) and containing at least one benzenoid-type ring and preferably containing from 6 to 15 carbon atoms (e.g., phenyl and naphthyl).

The term "aralkyl" represents an aryl group attached to the adjacent atom by an alkyl (e.g., benzyl).

The term "alkoxyalkyl" represents an alkoxy group attached to the adjacent group by an alkyl group (e.g., methoxymethyl).

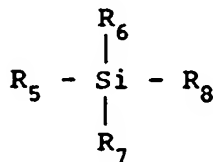
50 The term "aryloxy" represents a substituted (by a halogen, trifluoromethyl or C₁₋₅ alkoxy) or unsubstituted aryl moiety covalently bonded through an oxygen atom (e.g., phenoxy).

The term "acyl" refers to a radical derived from a carboxylic acid, substituted (by a halogen (F, Cl, Br, I), C₆₋₂₀ aryl or C₁₋₆ alkyl) or unsubstituted, by replacement of the -OH group. Like the acid to which it is related, an acyl radical may be aliphatic or aromatic, substituted (by a halogen, C₁₋₅ alkoxyalkyl, nitro or O₂) or unsubstituted, and whatever the structure of the rest of the molecule may be, the properties of the functional group remain essentially the same (e.g., acetyl, propionyl, isobutanoyl, pivaloyl, hexanoyl, trifluoroacetyl, chloroacetyl, and cyclohexanoyl).

55 A key feature of the processes of this invention is the use of a substituted carbonyl or carbonyl derivative as R₃ instead of a protected hydroxymethyl group as previously described in the art. Surprisingly, the substituted carbonyl or carbonyl derivative is not cleaved by exposure to a Lewis acid, as would have been expected by one of skill in the art when a Lewis acid of formula (III) is added to a mixture of silylated purine or pyrimidine base and the sugar compound

of formula (II). Instead, the substituted carbonyl/carbonyl derivative in the intermediate of formula (VI) forces the purine or pyrimidine base (R_2) to add in the *cis*-configuration relative to the substituted carbonyl/carbonyl derivative group. Without a substituted carbonyl or carbonyl derivative attached to C4' (for example, when a hydroxymethyl group is instead used), the coupling procedures described in Step 4 below will result in a mixture of *cis*- and *trans*-isomers.

Another key feature of the processes of this invention is the choice of Lewis acid. The Lewis acids used in the preparation of compounds of formula (I) have the general formula (III)



wherein R_5 , R_6 , R_7 and R_8 are as defined previously. These Lewis acids may be generated in situ or prepared using any method known in the art (e.g., A.H. Schmidt, "Bromotrimethylsilane and Iodotrimethylsilane-Versatile Reagents for Organic Synthesis", *Aldrichimica Acta*, 14, pp. 31-38 (1981)). The preferred Lewis acids of this invention are iodotrimethylsilane and trimethylsilyl triflate. The preferred R_5 , R_6 and R_7 groups are methyl or iodine. The most preferred R_5 , R_6 and R_7 group is methyl. The preferred R_8 groups are iodine, chlorine, bromine or sulphonate esters. The most preferred R_8 groups are iodine and trifluoromethane sulphonate.

In the preferred process of this invention, *cis*- and *trans*-isomers of a sugar of formula (II)



are separated by fractional crystallization and the desired configurational isomer selected. The selected *cis*- or the *trans*-isomer may then be chemically resolved using a chiral auxiliary. The pure chiral auxiliary-sugar diastereomer is then coupled to a silylated purine or pyrimidine base in the presence of a Lewis acid to afford an optically active nucleoside of *cis*- configuration which is subsequently reduced to give a nucleoside of formula (I).

Schemes 1A and 1B depict this preferred process as applied to any nucleoside of formula (I).

SCHEME 1A

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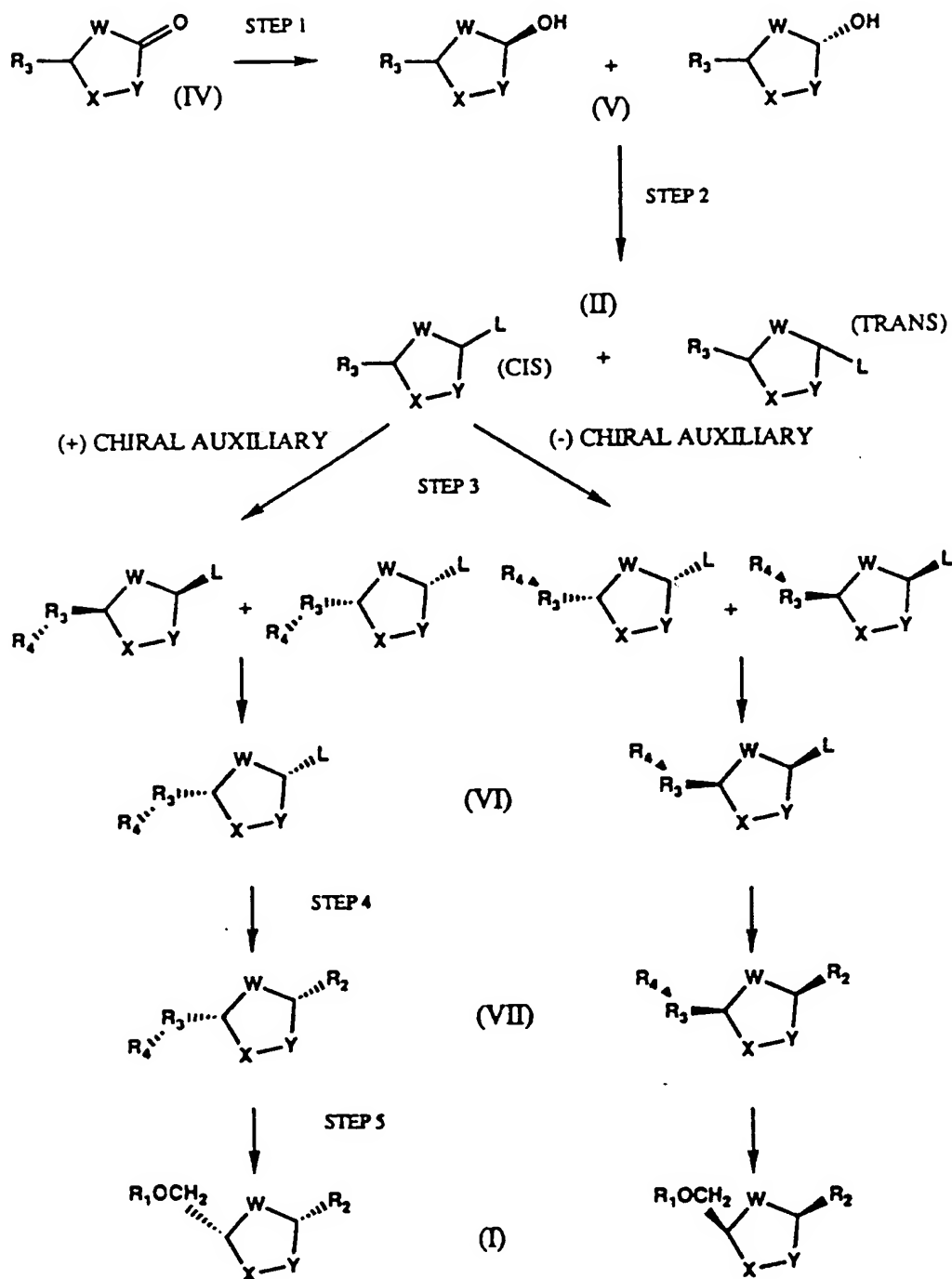
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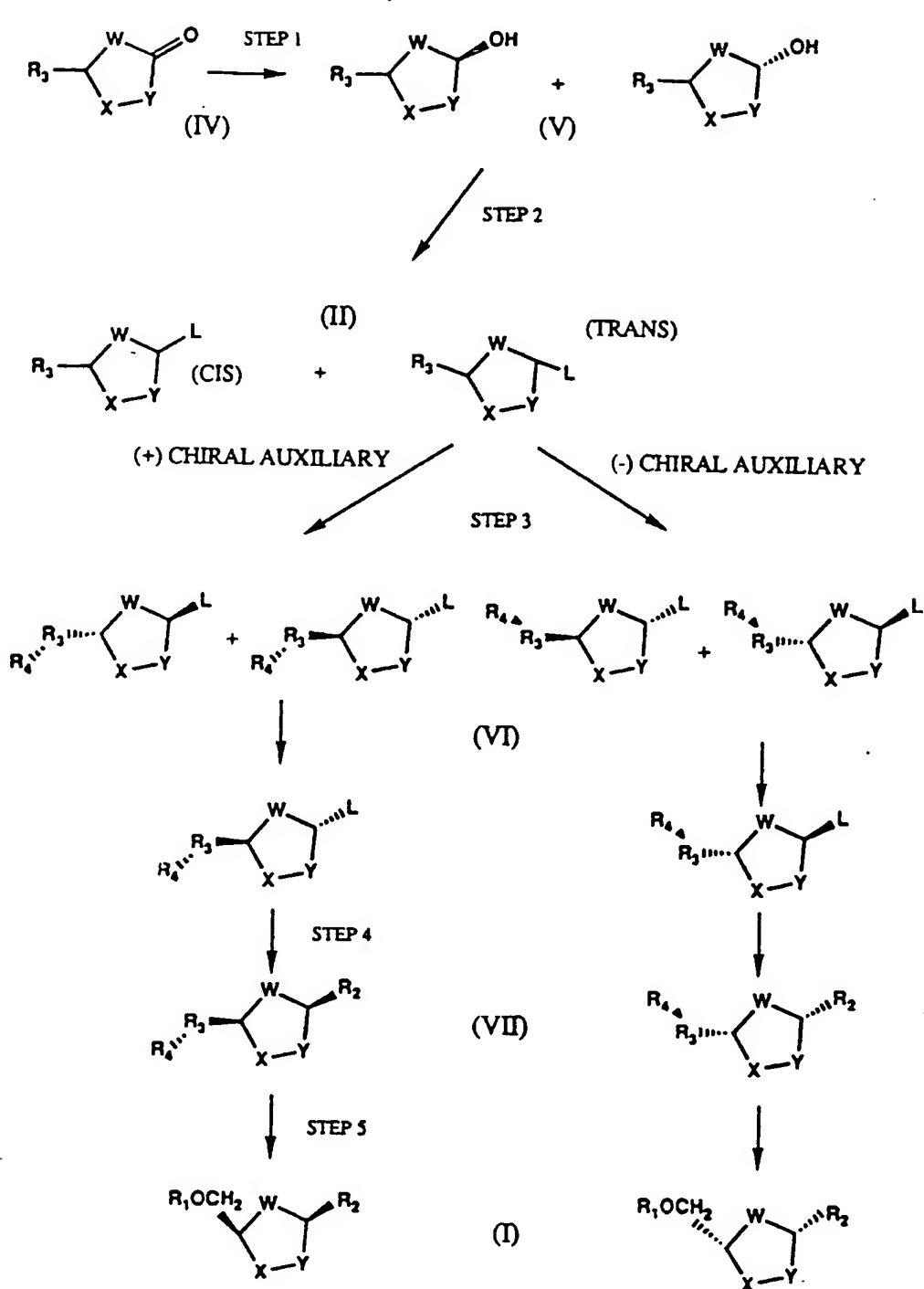
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SCHEME 1B



The various steps as illustrated in Schemes 1A and 1B may be briefly described as follows:

Step 1: The starting carbonyl-sugar of formula (IV) can be prepared by any method known in the art. E.g., Farina and Benigni, "A New Synthesis Of 2,3'-Dideoxy-nucleosides For Aids Chemotherapy", *Tetrahedron Letters*, 29, pp. 1239-

1242 (1988) and M. Okabe et al. "Synthesis Of The Dideoxynucleosides ddC and CNT From Glutamic Acid, Ribonolactone and Pyrimidine Bases", J. Org. Chem., 53, pp. 4780-4786 (1988). The carbonyl group of this starting compound is reduced chemoselectively with a suitable reducing agent, such as disiamylborane to give the *cis*- and *trans*-isomers of formula (V). Ordinarily, less *cis*-isomer is produced than *trans*.

5 Step 2: The hydroxyl group in the intermediate of formula (V) is readily converted to a leaving group by any method known in the art (e.g., T.W. Greene Protective Groups In Organic Synthesis, pp. 50-72, John Wiley & Sons, New York (1981)) to give the novel intermediates of formula (II).

This anomeric mixture is then separated by fractional crystallization into the two configurational isomers. The solvent may be adjusted to select for either the *cis*- or *trans*-isomer. D.J. Pasto and C.R. Johnson, Organic Structure Determination, pp. 7-10, Prentice-Hall, Inc., New Jersey (1969).

10 Step 3: Either the *cis*- (Scheme 1A) or *trans*-isomer (Scheme 1B) of formula (II) is chemically resolved using a chiral auxiliary (R_4). A suitable chiral auxiliary is one of high optical purity and where the mirror image is readily available, such as d- and l-menthol. The resulting diastereomers of formula (VI) are easily separated by fractional crystallization. Alternatively, either the *cis*- or the *trans*-isomer may be resolved enzymatically or by other methods known in the art. J. Jacques et al., Enantiomers, Racemates And Resolutions, pp. 251-369, John Wiley & Sons, New York (1981).

15 The optical purity of the diastereomer (VI, VII or I) can be determined by chiral HPLC methods, specific rotation measurements and NMR techniques. If the opposite enantiomer is desired, it may be obtained by using the mirror image of the chiral auxiliary initially employed. For example, if the chiral auxiliary d-menthol produces a (+)-enantiomer nucleoside, its mirror image, l-menthol, will produce the (-)-enantiomer.

20 Step 4: A previously silylated (or silylated in situ) purine or pyrimidine base or analogue or derivative thereof is then glycosylated with the resulting pure diastereomer in the presence of a Lewis acid of formula (III), such as iodotrimethylsilane (TMSI) or trimethylsilyl triflate (TMSOTf), to give a nucleoside of *cis*-configuration of formula (VII). This nucleoside is optically active and is substantially free of the corresponding *trans*-isomer (i.e., it contains no more than 25%, preferably no more than 10% and more preferably no more than 5% of the *trans*-isomer). Coupling of the intermediate of formula (VI) to the purine or pyrimidine base in this step proceeds in higher yields with the *cis*-isomer.

25 The preferred silylating agent for pyrimidine bases is t-butyldimethylsilyl triflate. It is believed that the bulky t-butyl group increases yields by weakening the interaction between the Lewis acid and silylated pyrimidine base.

The preferred method of mixing reagents in Step 4 is to first add the chiral auxiliary-sugar of formula (VI) to the silylated purine or pyrimidine base. The Lewis acid of formula (III) is then added to the mixture.

30 Step 5: The *cis*-nucleoside obtained in Step 4 may then be reduced with an appropriate reducing agent to remove the chiral auxiliary and give a specific stereoisomer of formula (I). The absolute configuration of this stereoisomer corresponds to that of the nucleoside intermediate of formula (VII). As shown in Scheme 1, either the *cis*- (Scheme 1A) or the *trans*-isomers (Scheme 1B) obtained in Step 2 will yield a *cis* end product.

35 A second process for the diastereoselective synthesis of compounds of formula (I) is illustrated by Scheme 2. The process of Scheme 2 is useful when optically pure starting material may be readily obtained commercially or easily prepared by known methods.

40 The optically active starting material is chemoselectively reduced and the resulting hydroxyl group converted to a leaving group. The diastereomeric mixture may be carried on further to compounds of formula (I) in a manner analogous to that described in Scheme 1. Optionally, the diastereomeric mixture may be separated by fractional crystallization and each isolated optically active diastereomer may be carried on further to compounds of formula (I).

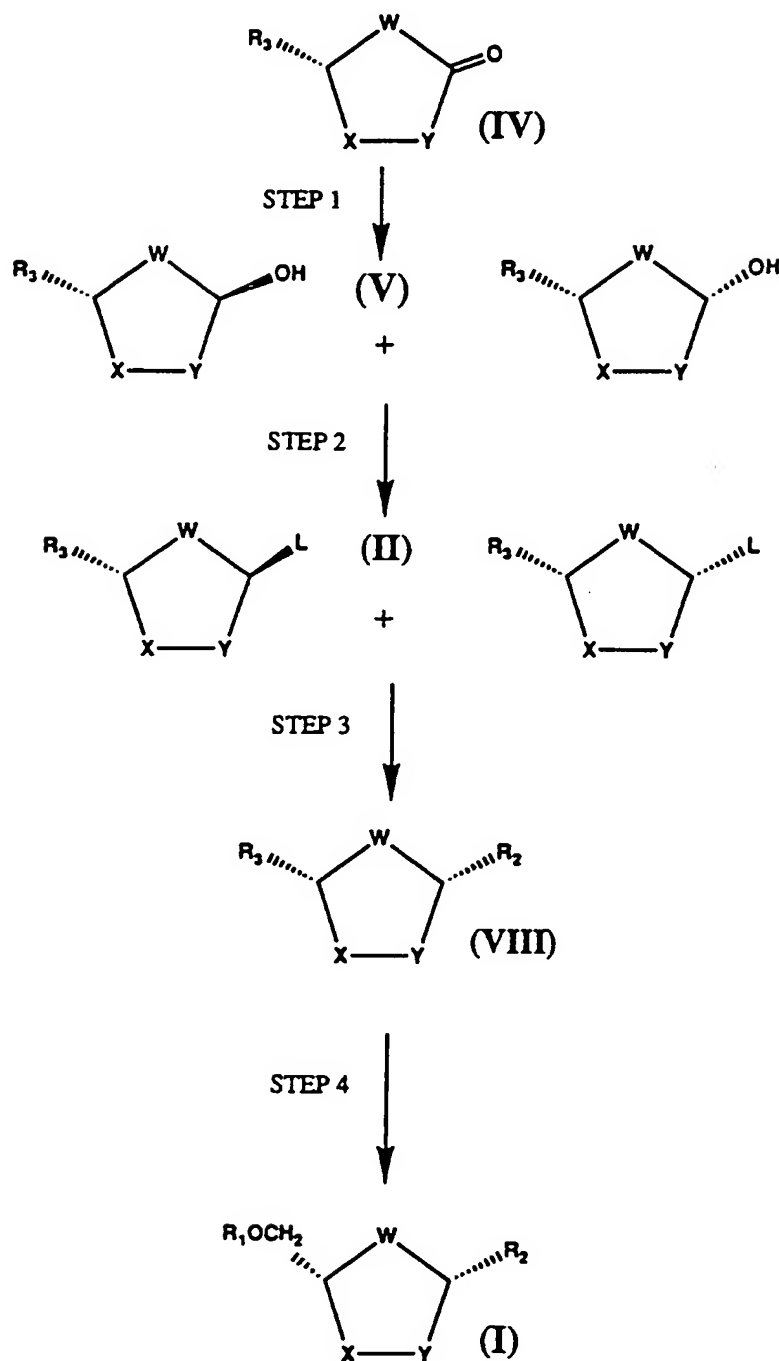
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Scheme 2 depicts the second process of this invention as applied to any nucleoside.

SCHEME 2



The various steps involved in the synthesis of the nucleosides of formula (I) as depicted in Scheme 2 may be briefly described as follows:

Step 1: The starting material of formula (IV) may be obtained commercially in optically pure form or prepared according

to the procedures of Farina and Benigni, "A New Synthesis Of 2,3'-Dideoxy-nucleosides For Aids Chemotherapy", Tetrahedron Letters, 29, pp. 1239-1242 (1988) and M. Okabe et al. "Synthesis Of The Dideoxynucleosides ddC and CNT From Glutamic Acid, Ribonolactone and Pyrimidine Bases", J. Org. Chem., 53, pp. 4780-4786 (1988). The single isomer of formula (IV) is chemoselectively reduced by a suitable reducing agent, such as disiamylborane to give a mixture of two diastereomers of formula (V).

Step 2: The hydroxyl groups of the two diastereomers of formula (V) are converted to leaving groups by any method known in the art to give a mixture of two diastereomers of formula (II).

Step 3: The diastereomeric mixture of formula (II) is reacted with previously silylated (or silylated in situ) purine or pyrimidine base or analogue or derivative. Then, addition of a Lewis acid of formula (III), such as iodotrimethylsilane (TMSI) or trimethylsilyl triflate (TMSOTf) yields a nucleoside of *cis*-configuration of formula (VIII). This nucleoside is substantially free of the corresponding *trans*-isomer.

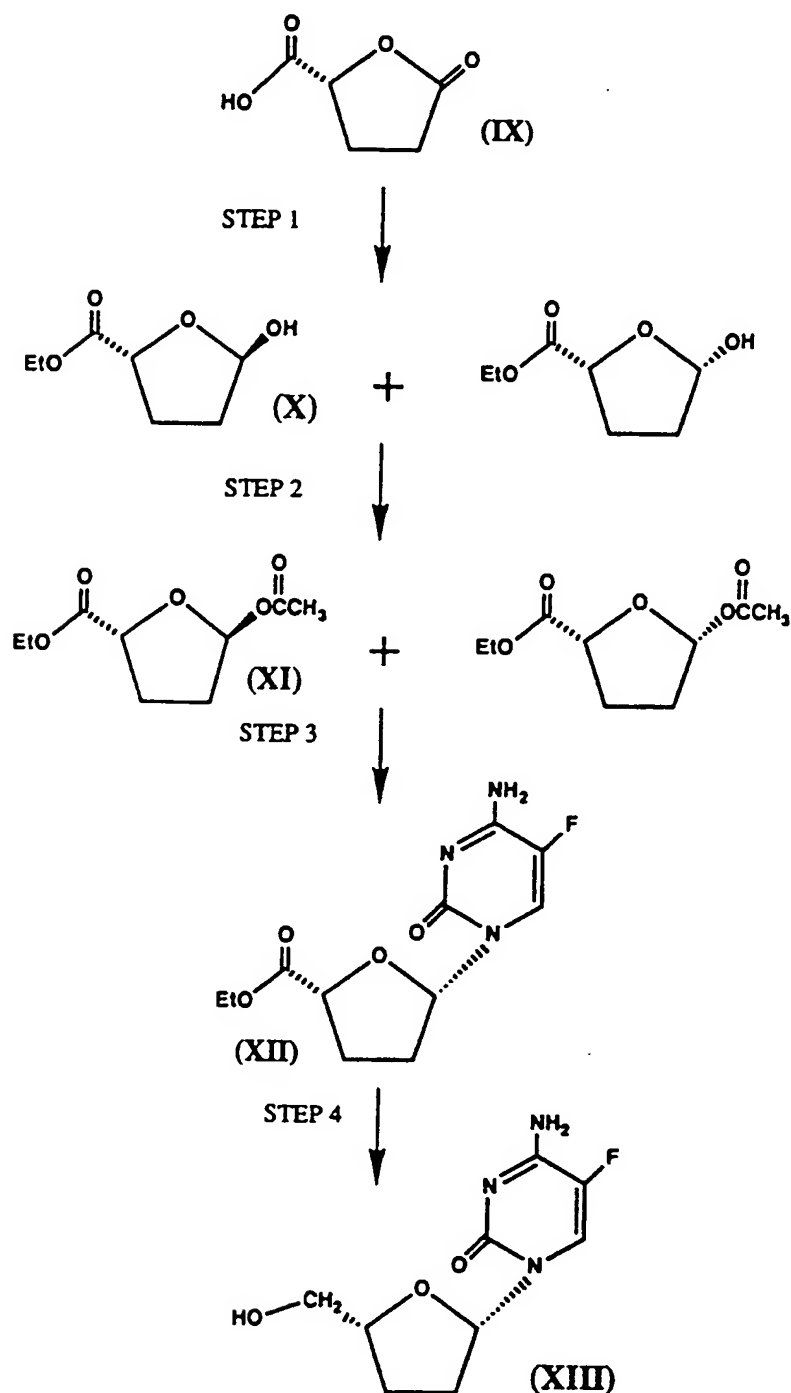
Step 4: The optically active *cis*-nucleoside of formula (VIII) is reduced stereospecifically with a reducing agent preferably lithium triethylborohydride or lithium aluminum hydride and more preferably sodium borohydride in an appropriate solvent such as tetrahydrofuran or diethyl ether to give the compound of formula (I).

Alternatively, at the end of Step 2, either the *cis*- or the *trans*-isomer may be separated out of the diastereomeric mixture of formula (II) by fractional crystallization or chromatography. The solvent may be adjusted to select for either the *cis*- or the *trans*-isomer. The single diastereomer of formula (II) would then be carried forward as described in Steps 3 and 4 to a compound of formula (I).

Schemes 3, 4 and 5 illustrate the application of the process of Scheme 2 to the synthesis of the enantiomers of *cis*-dideoxynucleoside analogues.

Although the process is illustrated using specific reagents and starting materials, it will be appreciated by one of skill in the art that suitable analogous reactants and starting materials may be used to prepare analogous compounds.

SCHEME 3



The various steps illustrated in Scheme 3 may be briefly described as follows:
 Step 1: The starting material (2R)-5-oxo-2-tetrahydrofuran carboxylic acid (IX) is available from commercial sources or

by synthesis from D-glutamic acid M. Okabe et al. "Synthesis Of The Dideoxynucleosides ddC and CNT From Glutamic Acid, Ribono-lactone and Pyrimidine Bases", J. Org. Chem., 53, pp. 4780-4786 (1988). The starting material is esterified with an alcohol such as ethanol in the presence of an acylating agent such as oxalyl chloride and an esterification catalyst such as 4-dimethylamino-pyrimidine and a base such as pyridine in a compatible solvent such as dichloromethane. The esterified compound is reduced with an appropriate reducing agent such as disiamylborane in a compatible organic solvent, such as tetrahydrofuran (A. Pelter et al., "Borane Reagents", Academic Press, p. 426 (1988)), to give the compounds of formula (X).

Step 2: The compounds of formula (X) is reacted with an acid chloride or acid anhydride, such as acetic anhydride, in the presence of pyridine and an acylation catalyst, such as 4-dimethylaminopyrimidine, to give the compounds of formula (XI).

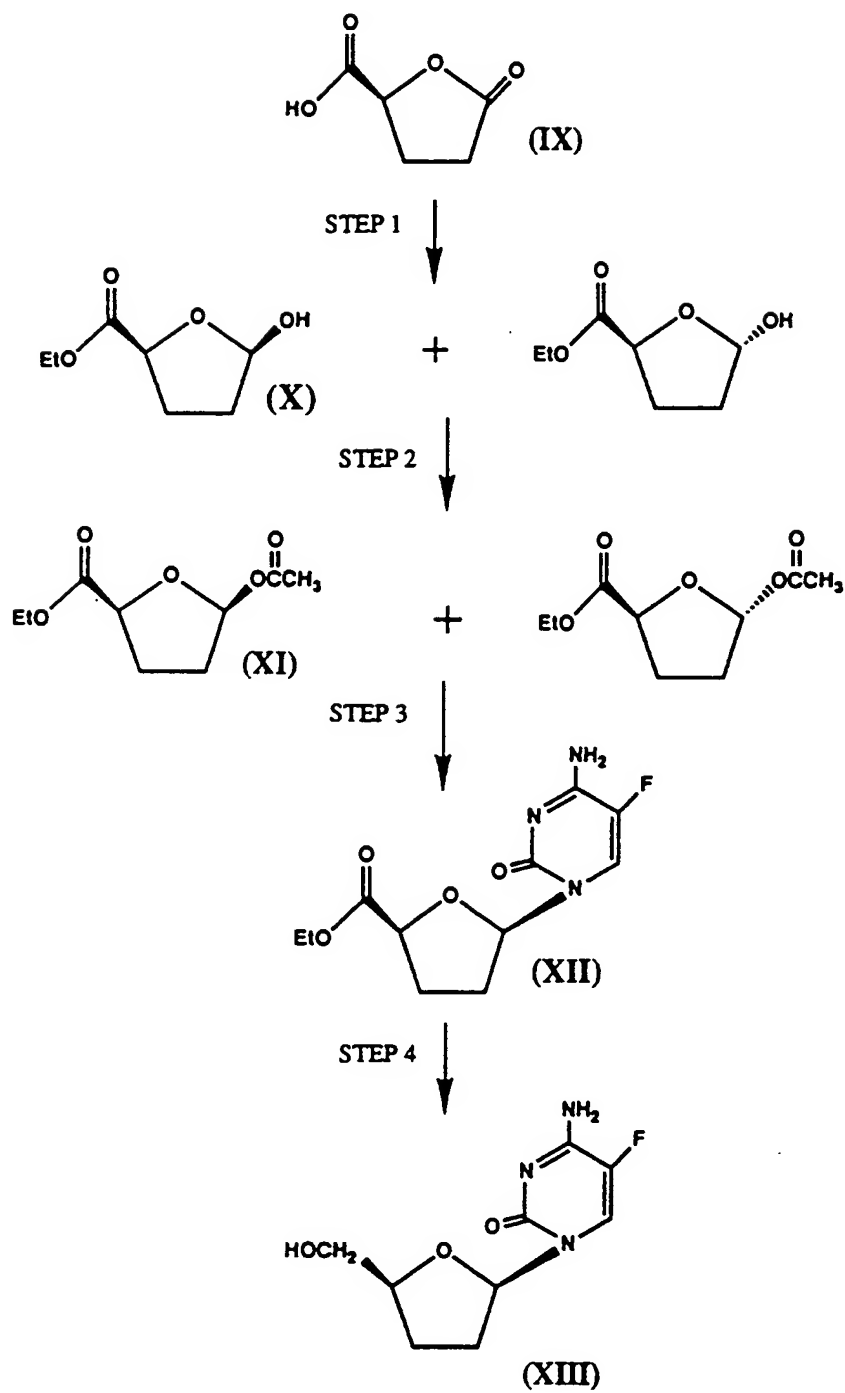
Step 3: The mixture of *cis*- and *trans*-acetoxy compound of formula (XI) is reacted with 5-fluorocytosine or other pyrimidine base or analogue thereof. The purine or pyrimidine base or analogue is preferably silylated with hexamethyldisilazane or more preferably silylated in situ with *t*-butyldimethylsilyl triflate in a compatible organic solvent, such as dichloromethane containing a hindered base, preferably 2,4,6-collidine.

A Lewis acid, preferably one derived from the compounds of formula (III), more preferably iodotrimethylsilane or trimethyl-silyl triflate, is then added to give the *cis* compound of formula (XII) in a highly diastereoselective manner.

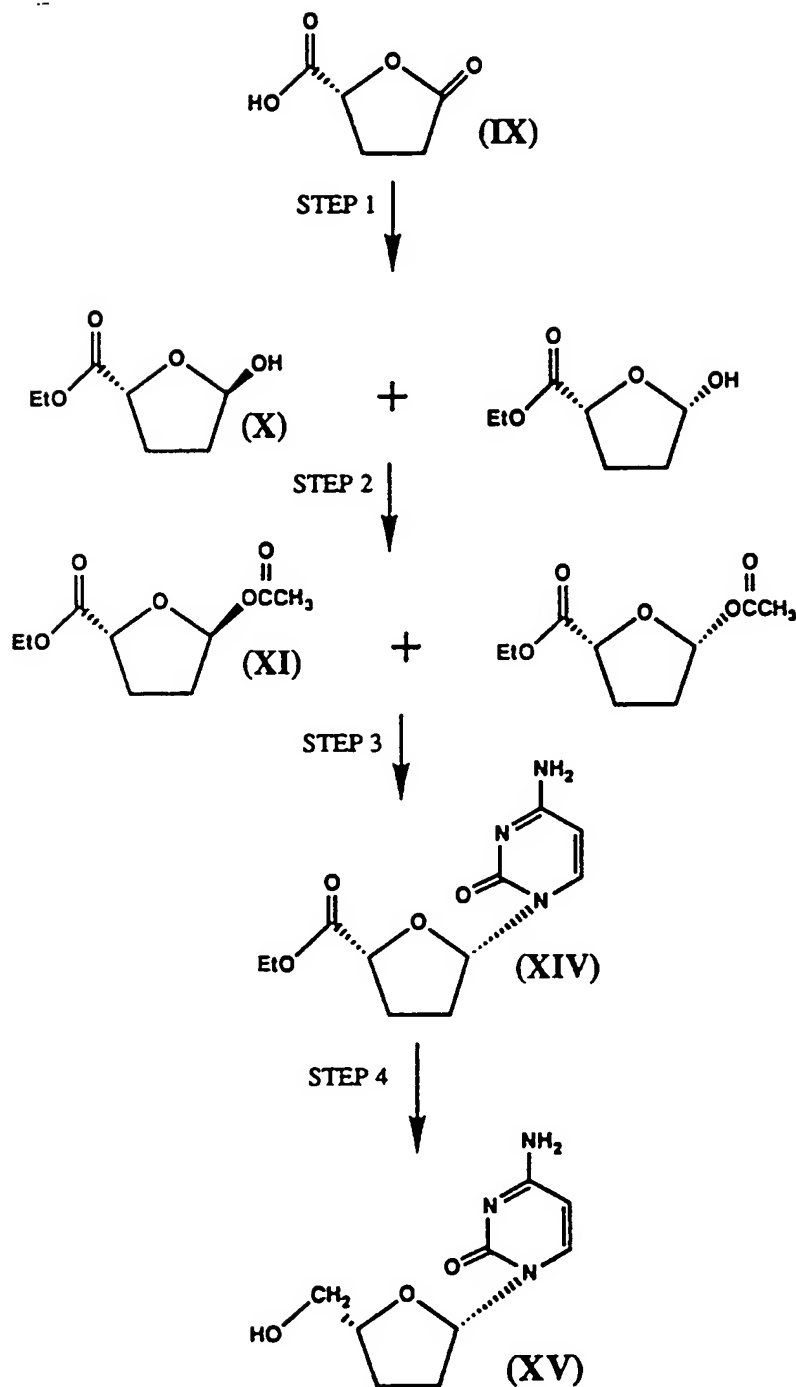
Step 5: The optically active *cis*-nucleoside (with some *trans*- isomer) of formula (XII) is reduced stereospecifically with a reducing agent, preferably sodium borohydride in an appropriate solvent, such as ethanol to give, after purification, the compound of formula (XIII).

It will be appreciated by one of skill in the art that if the enantiomer of formula (XIII) is desired, the starting material of formula (IX) would be (2S)-5-oxo-2-tetrahydrofuran carboxylic acid (Scheme 4) and the process would proceed just

as described for Scheme 3.

SCHEME 4

SCHEME 5



The various steps illustrated in Scheme 5 may be briefly described as follows:

Step 1: The starting material (2R)-5-oxo-2-tetrahydrofuran carboxylic acid (IX) is esterified with an alcohol such as ethanol in the presence of an acylating agent such as oxalyl chloride and an esterification catalyst such as 4-dimethylamino-

pyridimine and a base such as pyridine in a compatible solvent such as dichloromethane. The esterified compound is reduced with an appropriate reducing agent such as diisiamylborane in a compatible organic solvent, such as tetrahydrofuran to give the compounds of formula (X).

5 Step 2: The compounds of formula (X) is reacted with an acid chloride or acid anhydride, such as acetic anhydride, in the presence of pyridine and an acylation catalyst, such as 4-dimethylaminopyrimidine, to give the compounds of formula (XI).

10 Step 3: The mixture of *cis*- and *trans*-acetoxy compound of formula (XI) is reacted with N-acetyl cytosine or other pyrimidine base or analogue thereof. The purine or pyrimidine base or analogue is preferably silylated with hexamethyldisilazane or more preferably silylated in situ with trimethylsilyl triflate in a compatible organic solvent, such as dichloromethane containing a hindered base, preferably 2,4,6-collidine.

A Lewis acid, preferably one derived from the compounds of formula (III), more preferably iodotrimethylsilane, is then added to give *cis* nucleoside in a highly diastereoselective manner. The pure *cis*- nucleoside is obtained by trituration with an appropriate solvent such as ethyl acetate and hexanes.

15 The N-acetyl group is hydrolyzed preferably under acidic conditions and more preferably with trifluoroacetic acid in a compatible organic solvent such as isopropanol, preferably under reflux, to give the deacylated compounds of formula (XIV).

Step 4: The optically active *cis*-nucleoside of formula (XIV) is reduced stereospecifically with a reducing agent, preferably sodium borohydride in an appropriate solvent, such as ethanol to give the compound of formula (XV).

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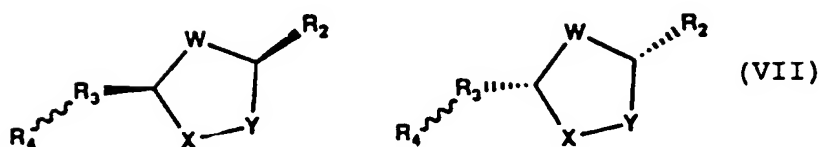
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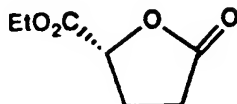
In the diastereoselective processes of this invention, the following intermediates are of particular importance:



wherein R_3 , R_4 and L are as defined above and provided that in intermediates of formula (VIII), when X is CHN_3 , then R_2 is not adenine or an analogue or derivative of adenine;

45 *cis* and *trans*-2R-carboethoxy-5-hydroxytetrahydrofuran;
cis and *trans*-2S-carboethoxy-5-hydroxytetrahydrofuran;
cis and *trans*-2R-carboethoxy-5-acetoxytetrahydrofuran;
cis and *trans*-2S-carboethoxy-5-acetoxytetrahydrofuran;
 50 1'S-(N-4-acetylcytosin-1-yl)-4'R-carboethoxytetrahydrofuran;
 1'S-(cytosin-1-yl)-4'R-carboethoxytetrahydrofuran;
 1'R-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran and 1'S-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran; and
 1'S-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran and 1'R-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran.

55 The following examples illustrate the present invention in a manner of which it can be practiced but, as such, should not be construed as limitations upon the overall scope of the processes of this invention. Except where specifically noted, all $[\alpha]_D$ measurements were recorded at ambient temperature.

Example 12R-CARBOETHOXY-5-OXO-TETRAHYDROFURAN

To a cold (0°C) stirred solution of 5-oxo-2R-tetrahydrofurancarboxylic acid (3 g, 23 mmol), 4-dimethylaminopyridine (141 mg, 0.05 equivalents), and pyridine (3.92 mL, 2.1 equivalents) in dichloromethane (15 mL) under an argon atmosphere was added oxalyl chloride (2.11 mL, 1.05 equivalents) over a period of 30 minutes. The cooling bath was removed and the reaction mixture was stirred at room temperature for 10 minutes. Ethanol (2.0 mL, 1.5 equivalents) was introduced and stirring was continued for another 1 hour 40 minutes. The reaction mixture was diluted with water and dichloromethane, followed by stirring for 10 minutes. The resultant mixture was transferred to a separatory funnel. The aqueous phase was removed and the organic layer was washed with 1 M HCl, saturated NaHCO₃, brine, and then was dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the crude product thus obtained was subjected to column chromatography (1:1 EtOAc-Hexane) to afford 3.23 g of the desired product as a syrup. ¹H NMR (CDCl₃): δ 1.28 (t, 3H, J=7.1 Hz), 2.20-2.40 (m, 1H), 4.23 (d of q 2H, J=0.9, 7.1 Hz), 4.86-4.96 (m 1H).

Example 2CIS AND TRANS-2R-CARBOETHOXY-5-HYDROXYTETRAHYDROFURAN

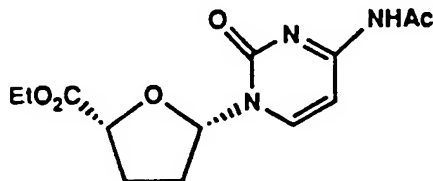
A solution of disiamylborane was prepared by mixing 35 mL of BH₃ THF (1 M in THF) and 35 mL of 2-methyl-2-butene (2 M in THF) at 0°C followed by stirring at 0°C for 75 minutes. To this solution was introduced 2R-carboethoxy-5-oxotetrahydrofuran dissolved in THF (6 mL). The resultant mixture was allowed to warm slowly to room temperature over a period of 2.5 hours and then was stirred for another 15 hours. Saturated ammonium chloride solution was added, followed by dilution with EtOAc. The above mixture was stirred for 10 minutes and then was transferred to a separatory funnel. The organic phase was washed successively with saturated NH₄Cl, brine, and then was dried (Na₂SO₄). The solvent was removed on a rotary evaporator and the crude product obtained was purified by column chromatography (40% EtOAc-Hexanes). The desired products were isolated in 70% yield (2.05 g) as a 2:3 mixture of isomer epimeric at C5. Trace amount of the open form isomer was also detected (¹H NMR). The title compounds displayed the following spectral characteristics: ¹H NMR (CDCl₃): δ 1.28 (t, 2H, J=7.1 Hz), 1.30 (t, 1H, J=7.1 Hz), 1.85-2.70 (m, 4H), 2.59 (d, 0.33H, J=5.5 Hz), 2.88 (d, 0.67H, J=3.1 Hz), 4.15-4.65 (m, 2H), 4.57 (d of d, 0.33H, J=6.4, 8.3 Hz), 4.70 (d of d, 0.67H, J=4.1, 8.7 Hz), 5.59 (m, 0.33H), 5.74 (m, 0.67H).

Example 3

CIS AND TRANS-2R-CARBOETHOXY-5-ACETOXYTETRAHYDROFURAN

To a cold (-78°C) stirred solution of a 2:3 mixture of *cis* and *trans*-2R-carboethoxy-5-hydroxytetrahydrofuran (2.04 g, 12.75 mmol), pyridine (1.24 mL, 1.2 equivalents), and 4-dimethylaminopyridine (16 mg, 0.01 equivalent) in dichloromethane (20 mL) was added acetyl chloride (1.09 mL, 1.2 equivalents) over a period of 5 minutes. The resultant mixture was stirred for 10 minutes. The -78°C cooling bath was then replaced with an ice-water bath. Stirring was continued for 4.5 hours while the bath temperature was allowed to warm slowly to room temperature. The reaction mixture was diluted with dichloromethane and then was transferred to a separatory funnel. The organic layer was washed successively with water, 1 M HCl, saturated NaHCO₃, brine and then was dried (Na₂SO₄). The solvent was removed on a rotary evaporator and the crude product obtained was purified by column chromatography (40% EtOAc-Hexane) to provide 1.757 g of the title compounds (a 5:4 mixture) as a thick oil. ¹H NMR (CDCl₃); δ 1.28 (t, 1.68H, J=7.1 Hz), 1.29 (t, 1.32H, J=7.1 Hz), 1.90-2.30 (m, 3H), 2.30-2.50 (m, 1H), 4.10-4.30 (m, 2H), 4.59 (t, 0.44H, J=8.0 Hz), 4.70 (d of d, 0.56H, J=3.2, 8.9 Hz), 6.33 (d of d, 0.44H, J=1.1, 3.9 Hz), 6.46 (d, 0.56H, J=4.5 Hz).

Example 4

1'S-(N-4-ACETYLCYTOSIN-1-YL)-4'R-CARBOETHOXYTETRAHYDROFURAN

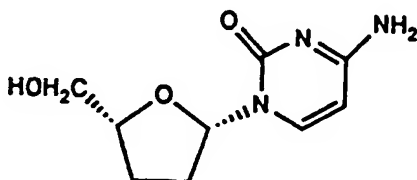
To a stirred suspension of N-4-acetylcytosine (50 mg, 0.298 mmol) in dichloromethane (0.75 mL) containing 2,6-lutidine (35 µL, 0.298 mmol) under an argon atmosphere was added trimethylsilyl trifluoromethanesulphonate (58 µL, 0.298 mmol). The resulting mixture was stirred for 15 minutes to give a light suspension. A solution of a 5:4 mixture of *cis*- and *trans*-2R-carboethoxy-5-acetoxytetrahydrofuran (50 mg, 0.248 mmol) in dichloromethane (1 mL) and iodotrimethylsilane (35 µL, 0.248 mmol) was sequentially introduced into the above suspension to generate a homogeneous solution. The reaction was allowed to proceed at room temperature for 1 hour and 40 minutes and then was quenched with a half-saturated solution of Na₂S₂O₃. The resulting mixture was stirred for 5 minutes and then was transferred to a separatory funnel with the aid of more dichloromethane. The aqueous phase was removed and the organic layer was washed with saturated Na₂S₂O₃, water, brine and then was dried (Na₂SO₄). The combined aqueous washings were reextracted with dichloromethane. The organic extracts were combined and concentrated under reduced pressure to provide 83 mg of the crude product. ¹H NMR analysis of the crude product indicated that a *cis* and *trans* (4:1) mixture of the expected nucleosides was generated. The crude product was dissolved in a minimum amount of chloroform. Addition of a 3:7 mixture of EtOAc-hexanes into this solution produced a white precipitate which was collected by suction filtration. Drying of this solid under vacuum afforded 25 mg (32%) of the title compound. ¹H NMR (CDCl₃); δ 1.33 (t, 3H,

J=7.1 Hz), 1.90-2.08 (m, 1H), 2.08-2.30 (m, 1H), 2.23 (s, 3H), 4.20-4.40 (m, 2H), 4.64 (t, 1H, J=7.2 Hz), 6.15 (d of d, 1H, J=4.0, 5.9 Hz), 7.46 (d, 1H, J=7.5 Hz), 8.34 (br s, 1H), 8.82 (d, 1H, J=7.5 Hz).

The washing was concentrated to give 58 mg of a *cis* and *trans* mixture (5:2) of the title compound and its 1' isomer.

Example 5

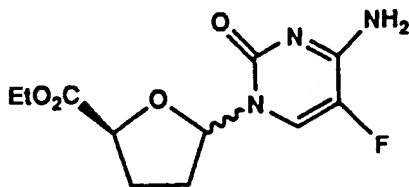
β -L-2',3'-DIDEOXYCYTIDINE



A mixture of 1'S-(N-4-acetylcytosin-1-yl)-4'R-carboethoxytetrahydrofuran (49 mg, 0.158 mmol, contains ca. 4% of the corresponding 1'R isomer) and trifluoroacetic acid (24 μ L, 2 equivalents) in ethanol (1 mL) was refluxed under an argon atmosphere for 2 hours and 40 minutes. The resultant mixture consisting of 1'S-(cytosine-1-yl)-4'R-carboethoxytetrahydrofuran and its 1' epimer was cooled to room temperature and then was diluted with ethanol (0.5 mL). Sodium borohydride (18 mg, 3 equivalents) was introduced and the reaction mixture was stirred for 1.5 hours. More reducing agent (6 mg) was added and stirring was continued for another 1 hour 20 minutes. The reaction was quenched by the addition of 2 drops of concentrated ammonium hydroxide followed by rigorous stirring for 15 minutes. The solvent was evaporated under reduced pressure and the crude product obtained was subjected to column chromatography (30% MeOH-EtOAc) to provide 28 mg (84%) of the title compound. The ^1H NMR spectrum of this material indicated the presence of ca. 3% of the corresponding 1'R isomer. This material was dissolved in a minimum amount of methanol. Addition of diethyl ether to this solution generated 20 mg (60%) of the title compound as a crystalline white precipitate free of the 1'R isomer (^1H NMR). The title compound displayed the following spectral characteristics: ^1H NMR (CD_3OD): δ 1.60-2.00 (m, 3H), 2.25-2.43 (m, 1H), 3.59 (d of d, 1H, J=4.1, 12.2 Hz), 3.78 (d of d, 1H, J=3.1, 12.2 Hz), 4.00-4.12 (m, 1H), 5.78 (d, 1H, J=7.4 Hz), 5.92 (d of d, 1H, J=3.1, 6.7 Hz), 8.02 (d, 1H, J=7.5 Hz).

Example 6

1'R-(5-FLUOROCYTOSIN-1-YL)-4'S-CARBOETHOXYTETRAHYDROFURAN AND 1'S-(5-FLUOROCYTOSIN-1-YL)-4'S-CARBOETHOXYTETRAHYDROFURAN

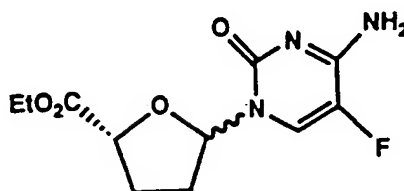


To a stirred suspension of 5-fluorocytosine (192 mg, 1.49 mmol) in dichloromethane (2 mL) containing 2,6-lutidine (346 μ L, 2.98 mmol) under an argon atmosphere was added *t*-butyldimethylsilyl trifluoromethanesulphonate 678 μ L, 2.98 mmol). The resulting mixture was stirred for 15 minutes to give a homogeneous solution. A solution of a 2:1 mixture of 2S-carboethoxy-5R-acetoxytetrahydrofuran and 2S-carboethoxy-5S-acetoxytetrahydrofuran (250 mg, 1.24 mmol) in dichloromethane (2 mL) and iodotrimethylsilane (176 μ L, 1.24 mmol) was sequentially introduced into the above solution.

The reaction was allowed to proceed at room temperature for 1 hour and 30 minutes and then was quenched with a half-saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$. The resulting mixture was stirred for 5 minutes and then was transferred to a separatory funnel. The aqueous phase was removed and the organic layer was washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$, water, brine and then was dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the crude product which was subjected to column chromatography (15% MeOH-EtOAc) to afford 199 mg (59%) of the title compounds as a mixture [7:1 (1'R,4'S):(1'S, 4'S) by ^1H NMR]. The product displayed the following spectral characteristics: ^1H NMR (CDCl_3): δ 1.15-1.40 (2 overlapping t, 3H), 1.90-2.15 (m, 2H), 2.25-2.55 (m, 2H), 4.15-4.35 (m, 2H), 4.54 (m, 0.87 Hz), 4.82 (d of d, 0.13H, $J=4.4$, 8.0 Hz), 5.70-6.80 (unresolved m, 1H), 6.09 (m, 1H), 7.40 (d, 0.13H, $J=6.7$ Hz), 7.90-8.60 (unresolved m, 1H), 8.48 (d, 0.87H, $J=6.7$ Hz).

Example 7

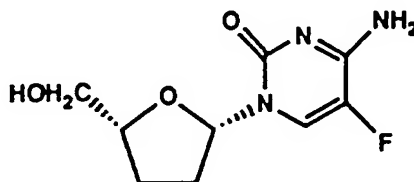
1'S-(5-FLUOROCYTOSIN-1-YL)-4'R-CARBOETHOXYTETRAHYDROFURAN AND 1'R-(5-FLUOROCYTOSIN-1-YL)-4'R-CARBOETHOXYTETRAHYDROFURAN



To a stirred suspension of 5-fluorocytosine (38 mg, 0.297 mmol) in dichloromethane (1 mL) containing 2,6-lutidine (69 μL , 0.594 mmol) under an argon atmosphere was added t-butyldimethylsilyl trifluoromethanesulphonate (137 μL , 0.594 mmol). The resulting mixture was stirred for 15 minutes to give a homogeneous solution. A solution of a 5:4 mixture of 2R-carboethoxy-5S-acetoxytetrahydrofuran and 2R-carboethoxy-5R-acetoxytetrahydrofuran (50 mg, 0.248 mmol) in dichloromethane (1 mL) and iodotrimethylsilane (35 μL , 0.248 mmol) was sequentially introduced into the above solution. The reaction was allowed to proceed at room temperature for 1 hour and 45 minutes and then was quenched with a half-saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$. The resulting mixture was stirred for 5 minutes and then was transferred to a separatory funnel. The aqueous phase was removed and the organic layer was washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$, water, brine and then was dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the crude product which was subjected to column chromatography (15% MeOH-EtOAc) to afford 52 mg (77%) of the title compounds as a 11:2 [(1'R,4'R):(1'S,4'R)] mixture (^1H NMR). The product displayed the following spectral characteristics: ^1H NMR (CDCl_3): δ 1.15-1.40 (2 overlapping t, 3H), 1.90-2.10 (m, 2H), 2.25-2.60 (m, 2H), 4.15-4.35 (m, 2H), 4.57 (m, 0.85 Hz), 4.84 (d of d, 0.15H, $J=4.2$, 7.8 Hz), 5.50-6.30 (unresolved m, 1H), 6.09 (m, 1H), 7.43 (d, 0.15H, $J=6.7$ Hz), 7.50-9.00 (unresolved m, 1H), 8.56 (d, 0.85H, $J=6.7$ Hz).

Example 8

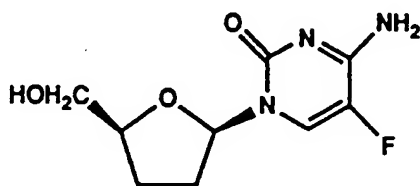
β -L-(5-FLUORO)-2',3'-DIDEOXYCYTIDINE



To a cold (0°C) stirred suspension of 1'R-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran and 1'S-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran [307 mg, 1.133 mmol, a 4:1 (1'R,4'R):(1'S, 4'R) mixture of the isomers] in 4 mL of ethanol was added sodium borohydride (86 mg, 2 equivalents). The resultant mixture was stirred for 5 minutes and the cooling bath was removed. Stirring was continued for 75 minutes at room temperature. The reaction was quenched by the addition of 4 drops of concentrated ammonium hydroxide. After the mixture had been stirred for 15 minutes, the solvent was removed under reduced pressure and the crude product was subjected to column chromatography (25% MeOH-EtOAc) to provide 197 mg (76%) of the expected 4'-hydroxymethyl products as a 4:1 mixture. One of the fractions collected was found to contain the title compound in 97% purity (¹H NMR). This fraction was concentrated to give 14 mg of a light beige coloured foam. UV (λ_{max}): 282.7, 236.4, 206.7 nm (MeOH); [α]_D-81° (c, 0.7 MeOH); ¹H NMR (CD₃OD): δ 1.77-1.90 (m, 2H), 1.90-2.03 (m, 1H), 2.25-2.42 (m, 1H), 3.61 (d of d, 1H, J=3.3, 12.3 Hz), 3.82 (d of d, 1H, J=2.8, 12.3 Hz), 4.06 (m, 1H), 5.87 (m, 1H), 8.32 (d, 1H, J=7.0 Hz).

Example 9

β -D-(5-FLUORO)-2',3'-DIDEOXYCYTIDINE



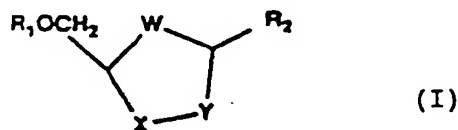
To a cold (0°C) stirred suspension of 1'R-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran and 1'S-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran [199 mg, 0.734 mmol, a 7:1 (1'R,4'S):(1'S, 4'S) mixture of the isomers] in 3 mL of ethanol was added sodium borohydride (56 mg, 2 equivalents). The resultant mixture was stirred for 5 minutes and the cooling bath was removed. Stirring was continued overnight (ca. 16 hours) at room temperature. The reaction was quenched by the addition of 4 drops of concentrated ammonium hydroxide. After the mixture has been stirred for 15 minutes, the solvent was removed under reduced pressure and the crude product was subjected to column chromatography (20% MeOH-EtOAc) to provide 112 mg (67%) of the expected 4'-hydroxymethyl products as a 7:1 (1'R,4'S):(1'S,4'S) mixture (¹H NMR). One of the fractions collected was found to contain the title compound only (¹H NMR). This fraction was concentrated *in vacuo* to give 27 mg of a white foam; UV (λ_{max}): 283.6, 238.2, 202.4 nm (MeOH); [α]_D+96° (c, 0.7 MeOH); ¹H NMR (CD₃OD): δ 1.77-1.90 (m, 2H), 1.90-2.03 (m, 1H), 2.25-2.42 (m, 1H), 3.61 (d of d, 1H, J=3.3, 12.3 Hz), 3.82 (d of d, 1H, J=2.8, 12.3 Hz), 4.06 (m, 1H), 5.87 (m, 1H), 8.32 (d, 1H, J=7.0 Hz).

While we have presented a number of embodiments of our invention, many alternatives, modifications and variations of these embodiments will be apparent to those of ordinary skill in the art. Therefore, it will be appreciated that the scope of this invention is to be defined by the following claims, rather than the specific examples presented above.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, GR, IT, LU, MC, NL, PT, SE

1. A diastereoselective process for producing optically active *cis*-nucleosides and nucleoside analogues and derivatives of formula (I)



wherein

R_1 is hydrogen or acyl;

R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

W is S, S=O, or SO₂, O, NZ, or CH₂;

X is O, S, S=O, or SO₂, NZ, CH₂, CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH; and

Z is hydrogen, hydroxyl, alkyl or acyl;

provided that W is not O, S, S=O or SO₂ when Y is CH₂ and X is O, S, S=O or SO₂; and further provided that when X is CH then Y is also CH;

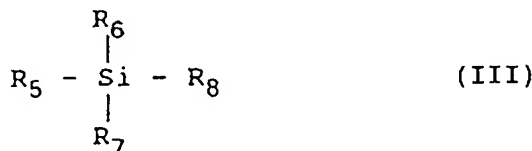
the process comprising the step of glycosylating the purine or pyrimidine base or analogue or derivative thereof with a single enantiomer of the compound of formula (II)



wherein

R_3 is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkylsiloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anyhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine; and

L is a leaving group,
using a Lewis acid of the formula (III)



wherein

R_5 , R_6 and R_7 are independently selected from the group consisting of hydrogen; C₁₋₂₀ alkyl optionally substituted by fluoro, bromo, chloro, iodo, C₁₋₆ alkoxy or C₆₋₂₀ aryloxy; C₇₋₂₀ aralkyl optionally substituted by halogen, C₁₋₂₀ alkyl or C₁₋₂₀ alkoxy; C₆₋₂₀ aryl optionally substituted by fluoro, bromo, chloro, iodo, C₁₋₂₀ alkyl or C₁₋₂₀ alkoxy; trialkylsilyl; fluoro; bromo; chloro and iodo; and

R_8 is selected from the group consisting of fluoro; bromo; chloro; iodo; C₁₋₂₀ sulphonate esters, optionally substituted by fluoro, bromo, chloro or iodo; C₁₋₂₀ alkyl esters optionally substituted by fluoro, bromo, chloro or iodo; polyvalent halides; trisubstituted silyl groups of the general formula (R₅)(R₆)(R₇)Si (wherein R₅, R₆, and R₇ are as defined above); saturated or unsaturated selenenyl C₆₋₂₀ aryl; substituted or unsubstituted C₆₋₂₀ arylsulfenyl; substituted or unsubstituted C₆₋₂₀ alkoxyalkyl; and trialkylsiloxy.

2. The process according to claim 1, further comprising the step of reducing R_3 of the glycosylated purine or pyrimidine base or analogue or derivative thereof to produce the optically active *cis*-nucleoside or nucleoside analogue or derivative of formula (I).
3. The process according to claim 1, further comprising the step of resolving the compound of formula (II) into a single enantiomer using a chiral auxiliary before glycosylating the purine or pyrimidine base.
4. The process according to any one of claims 1 to 3, wherein R_2 is a pyrimidine base.
5. The process according to claim 4, wherein the pyrimidine base is cytosine.

6. The process according to claim 4, wherein the pyrimidine base is 5-fluorocytosine.
7. The process according to any one of claims 1 to 3, wherein the Lewis acid is selected from the group consisting of trimethylsilyl triflate and iodotrimethylsilane.
8. The process according to claim 3, wherein the chiral auxiliary is selected from the group consisting of (d)-menthol and (l)-menthol.
9. The process according to any one of claims 1 to 3, wherein R_3 is selected from the group consisting of alkoxycarbonyl, carboxyls, diethylcarboxamide, pyrrolidine amide, methyl ketone and phenyl ketone.
10. The process according to claim 9, wherein the R_3 is selected from the group consisting of alkoxycarbonyl and carboxy.
11. An intermediate of formula (II)



wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

Z is hydrogen, hydroxyl, alkyl or acyl; provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂; and further provided that when X is CH then Y is also CH;

R_3 is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine; and

L is a leaving group.

12. An intermediate of formula (VI)



wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

Z is hydrogen, hydroxyl, alkyl or acyl;

provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂; and further provided that when X is CH then Y is also CH;

R_3 is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl,

or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine;

R₄ is a chiral auxiliary; and

L is a leaving group.

13. An intermediate of formula (VII)



wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂ CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

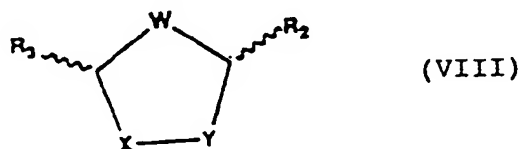
Z is hydrogen, hydroxyl, alkyl or acyl; provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂; and further provided that when X is CH then Y is also CH;

R₂ is a purine or pyrimidine base or an analogue or derivative thereof;

R₃ is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine; and

R₄ is a chiral auxiliary.

14. An intermediate of formula (VIII)



wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂ CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

Z is hydrogen, hydroxyl, alkyl or acyl;

provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂;

R₂ is a purine or pyrimidine base or an analogue or derivative thereof;

provided that when X is CH then Y is also CH, and when X is CHN₃, then R₂ is not adenine or an analogue or derivative of adenine; and

R₃ is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine.

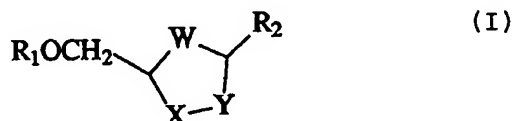
15. An intermediate selected from the group consisting of:

cis and *trans*-2R-carboethoxy-5-hydroxytetrahydrofuran;

cis and *trans*-2S-carboethoxy-5-hydroxytetrahydrofuran;
cis and *trans*-2R-carboethoxy-5-acetoxytetrahydrofuran;
cis and *trans*-2S-carboethoxy-5-acetoxytetrahydrofuran;
 1'S-(N-4-acetylcytosin-1-yl)-4'R-carboethoxytetrahydrofuran;
 1'S-(cytosin-1-yl)-4'R-carboethoxytetrahydrofuran;
 1'R-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran and 1'S-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran; and
 1'S-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran and 1'R-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran.

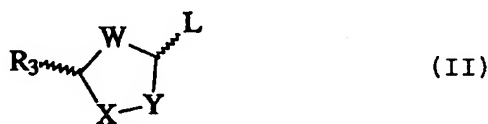
Claims for the following Contracting State : ES

1. A diastereoselective process for producing optically active *cis*-nucleosides and nucleoside analogues and derivatives of formula (I)



wherein

R₁ is hydrogen or acyl;
 R₂ is a purine or pyrimidine base or an analogue or derivative thereof;
 W is S, S=O, or SO₂, O, NZ, or CH₂;
 X is O, S, S=O, or SO₂, NZ, CH₂, CHF, CH, CHN₃, or CHOH;
 Y is O, S, CH₂, CH, CHF, or CHOH; and
 Z is hydrogen, hydroxyl, alkyl or acyl;
 provided that W is not O, S, S=O or SO₂ when Y is CH₂ and X is O, S, S=O or SO₂; and
 further provided that when X is CH then Y is also CH;
 the process comprising the step of glycosylating the purine or pyrimidine base or analogue or derivative thereof
 with a single enantiomer of the compound of formula (II)

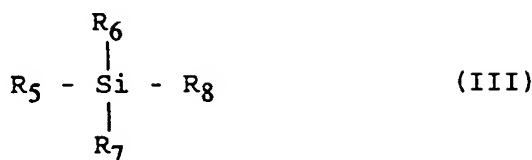


wherein

R₃ is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkylsiloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine; and

L is a leaving group,

using a Lewis acid of the formula (III)



wherein

R₅, R₆ and R₇ are independently selected from the group consisting of hydrogen; C₁₋₂₀ alkyl optionally substituted by fluoro, bromo, chloro, iodo, C₁₋₆ alkoxy or C₆₋₂₀ aryloxy; C₇₋₂₀ aralkyl optionally substituted by halogen, C₁₋₂₀ alkyl or C₁₋₂₀ alkoxy; C₆₋₂₀ aryl optionally substituted by fluoro, bromo, chloro, iodo, C₁₋₂₀ alkyl or C₁₋₂₀ alkoxy; trialkylsilyl; fluoro; bromo; chloro and iodo; and

R₈ is selected from the group consisting of fluoro; bromo; chloro; iodo; C₁₋₂₀ sulphonate esters, optionally substituted by fluoro, bromo, chloro or iodo; C₁₋₂₀ alkyl esters optionally substituted by fluoro, bromo, chloro or iodo; polyvalent halides; trisubstituted silyl groups of the general formula (R₅)(R₆)(R₇)Si (wherein R₅, R₆, and R₇ are as defined above); saturated or unsaturated selenenyl C₆₋₂₀ aryl; substituted or unsubstituted C₆₋₂₀ arylsulphenyl; substituted or unsubstituted C₆₋₂₀ alkoxyalkyl; and trialkylsiloxy.

2. The process according to claim 1, further comprising the step of reducing R₃ of the glycosylated purine or pyrimidine base or analogue or derivative thereof to produce the optically active *cis*-nucleoside or nucleoside analogue or derivative of formula (I).
3. The process according to claim 1, further comprising the step of resolving the compound of formula (II) into a single enantiomer using a chiral auxiliary before glycosylating the purine or pyrimidine base.
4. The process according to any one of claims 1 to 3, wherein R₂ is a pyrimidine base.
5. The process according to claim 4, wherein the pyrimidine base is cytosine.
6. The process according to claim 4, wherein the pyrimidine base is 5-fluorocytosine.
7. The process according to any one of claims 1 to 3, wherein the Lewis acid is selected from the group consisting of trimethylsilyl triflate and iodotrimethylsilane.
8. The process according to claim 3, wherein the chiral auxiliary is selected from the group consisting of (d)-menthol and (l)-menthol.
9. The process according to any one of claims 1 to 3, wherein R₃ is selected from the group consisting of alkoxycarbonyl, carboxyls, diethylcarboxamide, pyrrolidine amide, methyl ketone and phenyl ketone.
10. The process according to claim 9, wherein the R₃ is selected from the group consisting of alkoxycarbonyl and carboxy.
11. A process for producing an intermediate of formula (II)



wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

Z is hydrogen, hydroxyl, alkyl or acyl; provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O,

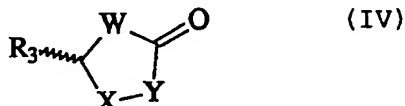
S, S=O or SO₂; and

further provided that when X is CH then Y is also CH;

R₃ is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine; and

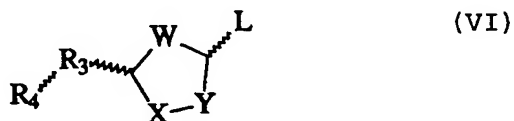
L is a leaving group;

comprising the step of chemoselectively reducing an intermediate of formula (IV):



and converting the resulting hydroxyl group to a leaving group, L.

12. A process for producing an intermediate of formula (VI)



wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂ CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

Z is hydrogen, hydroxyl, alkyl or acyl; provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂; and further provided that when X is CH then Y is also CH;

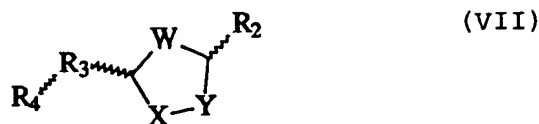
R₃ is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine;

R₄ is a chiral auxiliary; and

L is a leaving group; comprising the step of coupling an intermediate of formula (II) with a chiral auxiliary:



13. A process for producing an intermediate of formula (VII)



10 wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

X is O, S, S=O, SO₂, NZ, CH₂ CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

15 Z is hydrogen, hydroxyl, alkyl or acyl; provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂; and

further provided that when X is CH then Y is also CH;

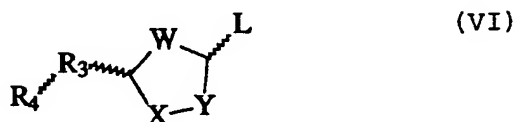
R₂ is a purine or pyrimidine base or an analogue or derivative thereof;

20 R₃ is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine;

25 and

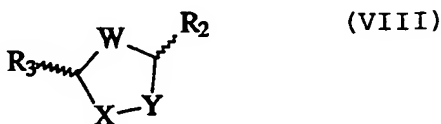
R₄ is a chiral auxiliary;

comprising the step of reacting an intermediate of formula (VI) with a silylated purine or pyrimidine base or an analogue or derivative thereof, R₂;



35 wherein L is a leaving group.

14. A process for producing an intermediate of formula (VIII)



45 wherein

W is O, S, S=O, SO₂, NZ, or CH₂;

50 X is O, S, S=O, SO₂, NZ, CH₂ CHF, CH, CHN₃, or CHOH;

Y is O, S, CH₂, CH, CHF, or CHOH;

Z is hydrogen, hydroxyl, alkyl or acyl; provided that when Y is CH₂ and X is O, S, S=O or SO₂, W is not O, S, S=O or SO₂;

R₂ is a purine or pyrimidine base or an analogue or derivative thereof;

55 provided that when X is CH then Y is also CH, and when X is CHN₃, then R₂ is not adenine or an analogue or derivative of adenine; and

R₃ is selected from the group consisting of carbonyl substituted with hydrogen, hydroxyl, trialkylsilyl, trialkyl-siloxy, C₁₋₃₀ alkyl, C₇₋₃₀ aralkyl, C₁₋₃₀ alkoxy, C₁₋₃₀ amine (primary, secondary or tertiary), C₁₋₃₀ thiol, C₆₋₂₀ aryl, C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl; 1,2-dicarbonyl, substituted with C₁₋₆ alkyl or C₆₋₂₀ aryl; anhydride substituted with

C₁₋₆ alkyl or C₆₋₂₀ aryl; azomethine substituted at nitrogen with hydrogen, C₁₋₂₀ alkyl or C₁₋₁₀ alkoxy or C₁₋₁₀ dialkylamino or at carbon with hydrogen, C₁₋₂₀ alkyl, or C₁₋₂₀ alkoxy; thiocarbonyl (C=S) substituted with hydroxyl, C₁₋₂₀ alkoxy, or C₁₋₂₀ thiol; homologues of carbonyl; homologues of thiocarbonyl and homologues of azomethine; comprising the step of reacting an intermediate of formula (II) with a silylated purine or pyrimidine base or an analogue or derivative thereof, R₂:



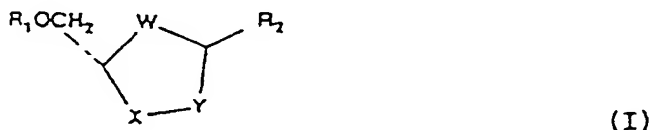
wherein L is a leaving group.

15. A process according to claim 11 or 14, wherein the produced intermediate is selected from the group consisting of:
- cis* and *trans*-2R-carboethoxy-5-hydroxytetrahydrofuran;
 - cis* and *trans*-2S-carboethoxy-5-hydroxytetrahydrofuran;
 - cis* and *trans*-2R-carboethoxy-5-acetoxytetrahydrofuran;
 - cis* and *trans*-2S-carboethoxy-5-acetoxytetrahydrofuran;
 - 1'S-(N-4-acetylcytosin-1-yl)-4'R-carboethoxytetrahydrofuran;
 - 1'S-(cytosin-1-yl)-4'R-carboethoxytetrahydrofuran;
 - 1'R-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran and 1'S-(5-fluorocytosin-1-yl)-4'S-carboethoxytetrahydrofuran; and
 - 1'S-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran and 1'R-(5-fluorocytosin-1-yl)-4'R-carboethoxytetrahydrofuran.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, GR, IT, LU, MC, NL, PT, SE

1. Einen diastereoselektiven Prozeß zur Produktion optisch aktiver *cis*-Nukleoside und Nukleosid-Analoga und -Derivate gemäß Formel (I)



wobei

R₁ ist Wasserstoff oder AzyI;

R₂ ist eine Purin- oder Pyrimidinbase oder ein Analogon oder Derivat davon;

W ist S, S=O oder SO₂, O, NZ oder CH₂;

X ist O, S, S=O oder SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;

Y ist O, S, CH₂, CH, CHF oder CHOH; und

Z ist Wasserstoff, Hydroxyl, Alky oder AzyI;

unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

den Prozeß, der den Schritt der Glykosylierung der Purin- oder Pyrimidinbase oder des Analogons oder Derivats davon mit einem einzigen Enantiomer der Verbindung gemäß Formel (II) enthält



wobei

R₃ ausgewählt wird aus der folgenden Gruppe: Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxo, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin; und

L ist eine abgehende Gruppe

unter Benutzung einer Lewissäure gemäß Formel (III)



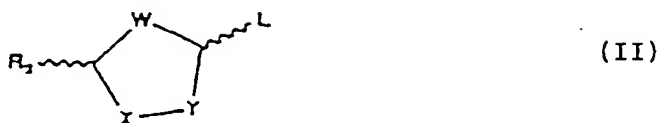
wobei

R₅, R₆ und R₇ ausgewählt werden aus der Gruppe bestehend aus Wasserstoff; C₁₋₂₀ Alkyl, wahlweise substituiert mit Fluor-, Brom-, Chlor-, Jod-, C₁₋₈ Alkoxy oder C₆₋₂₀ Aryloxy; C₇₋₂₀ Aralkyl, wahlweise substituiert mit Halogen, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; C₆₋₂₀ Aryl, wahlweise substituiert durch Fluor-, Brom-, Chlor-, Jod-, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Trialkylsilyl; Fluor-; Brom-; Chlor- und Jod-; und

R₈ wird ausgewählt aus der Gruppe bestehend aus Fluor-; Brom-; Chlor-; Jod-; C₁₋₂₀ Sulfonatester, wahlweise substituiert durch Fluor-, Brom-, Chlor- oder Jod-; C₁₋₂₀ Alkylester, wahlweise substituiert mit Fluor-, Brom-, Chlor- oder Jod-; polyvalente Halogenide; dreifachsubstituierte Silylgruppen der allgemeinen Formel (R₅)(R₆)(R₇)Si (wobei R₅, R₆ und R₇ wie oben definiert); gesättigtes oder ungesättigtes Selenyl C₆₋₂₀ Aryl; substituiertes oder nicht-substituiertes C₆₋₂₀ Arylsufenyl; substituiertes oder nichtsubstituierendes C₆₋₂₀ Alkoxyalkyl; und Trialkylsiloxo.

2. Den Prozeß gemäß Forderung 1 enthalte ferner den Schritt der Reduktion des R₃ der glykosylierten Purin- oder Pyrimidinbase bzw. des Analogons oder Derivats davon, um das optisch aktive cis-Nukleosid bzw. das Nukleosid-Analogon oder -Derivat gemäß Formel (I) hervorzubringen.
3. Den Prozeß gemäß Forderung 1 enthalte weiterhin den Schritt der Auflösung der Verbindung zur Formel (II) in ein einziges Enantiomer unter Benutzung einer chiralen Hilfssubstanz vor Glykosylierung der Purin- oder Pyrimidinbase.
4. Den Prozeß gemäß irgendeiner der Forderungen 1 bis 3, wobei R₂ eine Pyrimidinbase ist.
5. Den Prozeß gemäß Forderung 4, wobei die Pyrimidinbase Cytosin ist.
6. Den Prozeß gemäß Forderung 4, wobei die Pyrimidinbase 5-Fluorcytosin ist.
7. Den Prozeß gemäß irgendeiner der Forderungen 1 bis 3, wobei die Lewissäure ausgewählt wird aus der Gruppe bestehend aus Trimethylsilyltriflat und Jodtrimethylsilan.
8. Den Prozeß gemäß Forderung 3, wobei die chirale Hilfssubstanz ausgewählt wird aus der Gruppe bestehend aus (d)-Menthol und (l)-Menthol.
9. Den Prozeß gemäß irgendeiner der Forderungen 1 bis 3, wobei R₃ ausgewählt wird aus der Gruppe bestehend aus Alkoxy-carbonyl, Carboxyle, Diethylcarboxamid, Pyrrolidinamid, Methylketon und Phenylketon.
10. Den Prozeß gemäß Forderung 9, wobei R₃ ausgewählt wird aus der Gruppe bestehend aus Alkoxy-carbonyl und Carboxy.

11. Ein Zwischenprodukt gemäß Formel (II)



wobei

W ist O, S, S=O, SO₂, NZ oder CH₂;X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;Y ist O, S, CH₂, CH, CHF oder CHOH; und

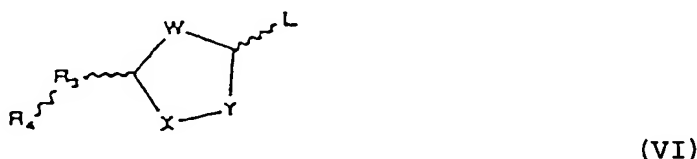
Z ist Wasserstoff, Hydroxyl, Alky oder Azy;

unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin; und

L ist eine abgehende Gruppe.

12. Ein Zwischenprodukt gemäß Formel (VI).



wobei

W ist O, S, S=O, SO₂, NZ oder CH₂;X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;Y ist O, S, CH₂, CH, CHF oder CHOH; und

Z ist Wasserstoff, Hydroxyl, Alky oder Azy;

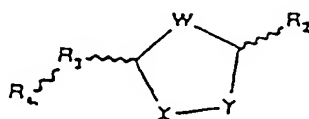
unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin;

R₄ ist eine chirale Hilfssubstanz; und

L ist eine abgehende Gruppe.

13. Ein Zwischenprodukt gemäß Formel (VII)



(VII)

wobei

W ist O, S, S=O, SO₂, NZ oder CH₂;X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;Y ist O, S, CH₂, CH, CHF oder CHOH; und

Z ist Wasserstoff, Hydroxyl, Alky oder Azyl;

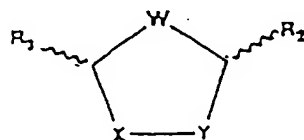
unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

R₂ ist eine Purin- oder Pyrimidinbase oder ein Analogon oder Derivat davon;

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin;

R₄ ist eine chirale Hilfssubstanz.

14. Ein Zwischenprodukt gemäß Formel (VIII)



(VIII)

wobei

W ist O, S, S=O, SO₂, NZ oder CH₂;X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;Y ist O, S, CH₂, CH, CHF oder CHOH; und

Z ist Wasserstoff, Hydroxyl, Alky oder Azyl;

unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂;

R₂ ist eine Purin- oder Pyrimidinbase oder ein Analogon oder Derivat davon;

unter der Bedingung, daß wenn X ist Ch, dann ist Y ebenfalls CH und wenn X ist CHN₃, dann ist R₂ nicht Adenin oder ein Analogon oder Derivat von Adenin; und

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin.

15. Ein Zwischenprodukt ausgewählt aus der Gruppe bestehend aus

cis und trans-2R-Carboethoxy-5-Hydroxytetrahydrofuran;

cis und trans-2S-Carboethoxy-5-Hydroxytetrahydrofuran;

cis und trans-2R-Carboethoxy-5-Azetoxytetrahydrofuran;

cis und trans-2S-Carboethoxy-5-Azetoxytetrahydrofuran;

1'S-(N-4-Azetylcytosin-1-yl)-4'R-Carboethoxytetrahydrofuran;

1'S-(Cytosin-1-yl)-4'R-Carboethoxytetrahydrofuran;

1'R-(5-Fluorocytosin-1-yl)-4'S-Carboethoxytetrahydrofuran und 1'S-(5-Fluorocytosin-1-yl)-4'S-Carboethoxy-

tetrahydrofuran; und

1'S-(5-Fluorcytosin-1-yl)-4'R-Carboethoxytetrahydrofuran und 1'R-(5-Fluorcytosin-1-yl)-4'R-Carboethoxytetrahydrofuran.

5 Patentansprüche für folgenden Vertragsstaat : ES

1. Einen diastereoselektiven Prozeß zur Produktion optisch aktiver *cis*-Nukleoside und Nukleosid-Analoga und -Derivate gemäß Formel (I)



wobei

R₁ ist Wasserstoff oder AzyI;

R₂ ist eine Purin- oder Pyrimidinbase oder ein Analogon oder Derivat davon;

W ist S, S=O oder SO₂, O, NZ oder CH₂;

X ist O, S, S=O oder SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;

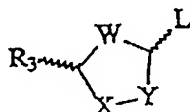
Y ist O, S, CH₂, CH, CHF oder CHOH; und

Z ist Wasserstoff, Hydroxyl, Alkyl oder AzyI;

unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

den Prozeß, der den Schritt der Glykosylierung der Purin- oder Pyrimidinbase oder des Analogons oder Derivats davon mit einem einzigen Enantiomer der Verbindung gemäß Formel (II) enthält

(II)



wobei

R₃ ausgewählt wird aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin; und

L ist eine abgehende Gruppe;

unter Benutzung einer Lewissäure gemäß Formel (III)



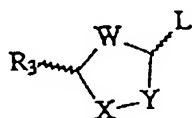
wobei

R₅, R₆ und R₇ ausgewählt werden aus der Gruppe bestehend aus Wasserstoff; C₁₋₂₀ Alkyl, wahlweise substituiert mit Fluor-, Brom-, Chlor-, Jod-, C₁₋₆ Alkoxy oder C₆₋₂₀ Aryloxy; C₇₋₂₀ Aralkyl, wahlweise substituiert mit Halogen, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; C₆₋₂₀ Aryl, wahlweise substituiert durch Fluor-, Brom-, Chlor-, Jod-, C₁₋₂₀

Alkyl oder C₁₋₂₀ Alkoxy; Trialkylsilyl; Fluor-; Brom-; Chlor- und Jod-; und

R₈ wird ausgewählt aus der Gruppe bestehend aus Fluor-; Brom-; Chlor-; Jod-; C₁₋₂₀ Sulfonatester, wahlweise substituiert durch Fluor-, Brom-, Chlor- oder Jod-; C₁₋₂₀ Alkylester, wahlweise substituiert mit Fluor-, Brom-, Chlor- oder Jod-; polyvalente Halogenide; dreifachsubstituierte Silylgruppen der allgemeinen Formel (R₅)(R₆)(R₇)Si (wobei R₅, R₆ und R₇ wie oben definiert); gesättigtes oder ungesättigtes Selenenyl C₆₋₂₀ Aryl; substituiertes oder nichtsubstituiertes C₆₋₂₀ Arylsufenyl; substituiertes oder nichtsubstituiertes C₆₋₂₀ Alkoxyalkyl; und Trialkylsiloxy.

2. Den Prozeß gemäß Forderung 1, der ferner den Schritt der Reduktion des R₃ der glykosylierten Purin- oder Pyrimidinbase bzw. des Analogons oder Derivats davon enthalte, um das optisch aktive cis-Nukleosid bzw. das Nukleosid-Analogon oder -Derivat gemäß Formel (I) hervorzubringen.
3. Den Prozeß gemäß Forderung 1, der weiterhin den Schritt der Auflösung der Verbindung zur Formel (II) in ein einziges Enantiomer unter Benutzung einer chiralen Hilfssubstanz vor Glykosylierung der Purin- oder Pyrimidinbase enthalte.
4. Den Prozeß gemäß irgendeiner der Forderungen 1 bis 3, wobei R₂ eine Pyrimidinbase ist.
5. Den Prozeß gemäß Forderung 4, wobei die Pyrimidinbase Cytosin ist.
6. Den Prozeß gemäß Forderung 4, wobei die Pyrimidinbase 5-Fluorcytosin ist.
7. Den Prozeß gemäß irgendeiner der Forderungen 1 bis 3, wobei die Lewissäure ausgewählt wird aus der Gruppe bestehend aus Trimethylsilyltriflat und Jodtrimethylsilan.
8. Den Prozeß gemäß Forderung 3, wobei die chirale Hilfssubstanz ausgewählt wird aus der Gruppe bestehend aus (d)-Menthol und (l)-Menthol.
9. Den Prozeß gemäß irgendeiner der Forderungen 1 bis 3, wobei R₃ ausgewählt wird aus der Gruppe bestehend aus Alkoxy-carbonyl, Carboxyle, Diethylcarboxamid, Pyrrolidinamid, Methylketon und Phenylketon.
10. Den Prozeß gemäß Forderung 9, wobei R₃ ausgewählt wird aus der Gruppe bestehend aus Alkoxy-carbonyl und Carboxy.
11. Einen Prozeß zur Herstellung eines Zwischenprodukts gemäß Formel (II)



(II)

wobei:

W ist O, S, S=O, SO₂, NZ oder CH₂;

X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;

Y ist O, S, CH₂, CH, CHF oder CHOH;

Z ist Wasserstoff, Hydroxyl, Alkyl oder Azyl;

unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin; und

L ist eine abgehende Gruppe;

den Schritt der chemoselektiven Reduktion eines Zwischenprodukts gemäß Formel (IV) enthaltend:



sowie zur Umwandlung der resultierenden Hydroxylgruppe in eine abgehende Gruppe, L

12. Einen Prozeß zur Herstellung eines Zwischenprodukts gemäß Formel (VI).



wobei

W ist O, S, S=O, SO₂, NZ oder CH₂;

X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;

Y ist O, S, CH₂, CH, CHF oder CHOH;

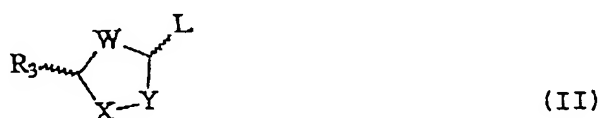
Z ist Wasserstoff, Hydroxyl, Alkyl oder Aeryl;

unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin;

R₄ ist eine chirale Hilfssubstanz; und

L ist eine abgehende Gruppe; den Schritt der Kopplung eines Zwischenprodukts gemäß Formel (II) mit einer chiralen Hilfssubstanz enthaltend:



13. Einen Prozeß zur Herstellung eines Zwischenprodukts gemäß Formel (VII)



wobei

W ist O, S, S=O, SO₂, NZ oder CH₂;

X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;

Y ist O, S, CH₂, CH, CHF oder CHOH;

Z ist Wasserstoff, Hydroxyl, Alkyl oder Azyll;

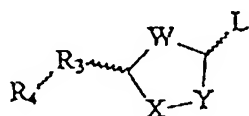
unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂; und unter der weiteren Bedingung, daß wenn X ist CH, dann Y ist ebenfalls CH;

R₂ ist eine Purin- oder Pyrimidinbase oder ein Analogon oder Derivat davon;

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin; und

R₄ ist eine chirale Hilfssubstanz;

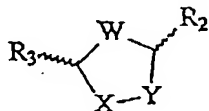
den Schritt der Reaktion eines Zwischenprodukts gemäß Formel (VI) mit einer silylierten Purin- oder Pyrimidinbase oder eines Analogons oder Derivats davon, R₂, enthaltend:



(VI)

worin L eine abgehende Gruppe ist.

14. Einen Prozeß zur Herstellung eines Zwischenprodukts gemäß Formel (VIII)



(VIII)

wobei

W ist O, S, S=O, SO₂, NZ oder CH₂;

X ist O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ oder CHOH;

Y ist O, S, CH₂, CH, CHF oder CHOH;

Z ist Wasserstoff, Hydroxyl, Alkyl oder Azyll;

unter der Bedingung, daß W nicht O, S, S=O oder SO₂ ist, wenn Y ist CH₂ und X ist O, S, S=O oder SO₂;

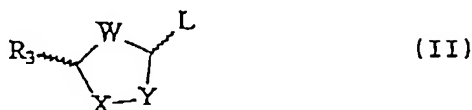
R₂ ist eine Purin- oder Pyrimidinbase oder ein Analogon oder Derivat davon;

unter der Bedingung, daß wenn X ist Ch, dann ist Y ebenfalls CH und wenn X ist CHN₃, dann ist R₂ nicht Adenin oder ein Analogon oder Derivat von Adenin; und

R₃ wird ausgewählt aus der Gruppe bestehend aus Carbonyl substituiert mit Wasserstoff, Hydroxyl, Trialkylsilyl, Trialkylsiloxy, C₁₋₃₀ Alkyl, C₇₋₃₀ Aralkyl, C₁₋₃₀ Alkoxy, C₁₋₃₀ Amin (primär, sekundär oder tertiär), C₁₋₃₀ Thiol, C₆₋₂₀ Aryl, C₁₋₂₀ Alkenyl, C₁₋₂₀ Alkynyl; 1,2-Dicarbonyl substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Anhydrid substituiert mit C₁₋₆ Alkyl oder C₆₋₂₀ Aryl; Azomethin substituiert am Stickstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₁₀ Alkoxy oder C₁₋₁₀ Dialkylamino oder am Kohlenstoff mit Wasserstoff, C₁₋₂₀ Alkyl oder C₁₋₂₀ Alkoxy; Thiocarbonyl (C=S) substituiert mit Hydroxyl, C₁₋₂₀ Alkoxy oder C₁₋₂₀ Thiol; Homologe von Carbonyl; Homologe von Thiocarbonyl und Homologe von Azomethin;

den Schritt der Reaktion eines Zwischenprodukts gemäß Formel (II) mit einer silylierten Purin- oder Pyrimidinbase

oder eines Analogons oder Derivats davon, R_2 , enthaltend:



wobei L eine abgehende Gruppe ist.

10 15. Einen Prozeß gemäß den Forderungen 11 oder 14, wobei das hergestellte Zwischenprodukt ausgewählt wird aus der Gruppe bestehend aus:

cis und *trans*-2R-Carboethoxy-5-Hydroxytetrahydrofuran;

cis und *trans*-2S-Carboethoxy-5-Hydroxytetrahydrofuran;

15 *cis* und *trans*-2R-Carboethoxy-5-Azetoxytetrahydrofuran;

cis und *trans*-2S-Carboethoxy-5-Azetoxytetrahydrofuran;

1'S-(N-4-Azetylcytosin-1-yl)-4'R-Carboethoxytetrahydrofuran;

1'S-(Cytosin-1-yl)-4'R-Carboethoxytetrahydrofuran;

20 1'R-(5-Fluorcytosin-1-yl)-4'S-Carboethoxytetrahydrofuran und 1'S-(5-Fluorcytosin-1-yl)-4'S-Carboethoxytetrahydrofuran; und

1'S-(5-Fluorcytosin-1-yl)-4'R-Carboethoxytetrahydrofuran und 1'R-(5-Fluorcytosin-1-yl)-4'R-Carboethoxytetrahydrofuran.

Revendications

25 Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, GR, IT, LU, MC, NL, PT, SE

1. Un procédé de synthèse diastéréosélective de *cis*-nucléosides optiquement actifs, d'analogues et de dérivés de nucléosides de formule (I) :



où

R_1 représente l'hydrogène ou un groupe acyle;

R_2 représente une base purique ou pyrimidique, ou un analogue ou un dérivé de cette base;

W représente S, S=O ou SO₂, O, NZ ou CH₂;

X représente O, S, S=O ou SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;

Y représente O, S, CH₂, CH, CHF ou CHOH; et

45 Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;

à condition que W ne soit ni O, ni S, ni S=O, ni SO₂, lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂;

et, en plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;

le procédé comprenant l'étape de glycosylation de la base purique ou pyrimidique, ou de l'analogue ou du dérivé de cette base, avec un seul énantiomère du composé de formule (II).



où

R_3 est l'un des groupes suivants : carbonyle substitué par l'hydrogène ou un groupe hydroxyle, trialkylsilyle,

trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S) substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine; et

L représente un groupe partant, utilisant un acide de Lewis de formule (III)



où R₅, R₆ et R₇ sont choisis indépendamment parmi les groupes suivants : hydrogène; alkyle C₁₋₂₀ pouvant être substitué par un groupe fluoro, bromo, chloro, iodo, alkoxy C₁₋₆ ou aryloxy C₆₋₂₀; aralkyle C₇₋₂₀ pouvant être substitué par un halogène, un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; aryle C₆₋₂₀ pouvant être substitué par un groupe fluoro, bromo, chloro, iodo, alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; trialkylsilyle; fluoro; bromo; chloro et iodo; et R₈ est sélectionné parmi les groupes suivants : fluoro; bromo; chloro; iodo; esters sulfonates C₁₋₂₀, pouvant être substitués par un groupe fluoro, bromo, chloro ou iodo; esters d'alkyle C₁₋₂₀, pouvant être substitués par un groupe fluoro, bromo, chloro ou iodo; halogénures polyvalents; silyles trisubstitués de formule générale (R₅)(R₆)(R₇)Si (où R₅, R₆ et R₇ ont été définis ci-dessus); aryle C₆₋₂₀ sélénényle saturé ou insaturé; arylsulfényle C₆₋₂₀ substitué ou non; alkoxyalkyle C₆₋₂₀ substitué ou non; et trialkylsiloxy.

2. Le procédé en vertu de la revendication n° 1, comprenant de plus l'étape de réduction du groupe R₃ de la base purique ou pyrimidique glycosylée, ou de l'analogue ou du dérivé de cette base glycosylée, visant à produire le *cis*-nucléoside optiquement actif, ou l'analogue ou le dérivé de ce nucléoside de formule (I).
3. Le procédé en vertu de la revendication n° 1, comprenant de plus l'étape de résolution du composé de formule (II) en un seul énantiomère, par l'utilisation d'un auxiliaire chiral, préalablement à la glycosylation de la base purique ou pyrimidique.
4. Le procédé en vertu de l'une ou l'autre des revendications n° 1 à 3, lorsque R₂ est une base pyrimidique.
5. Le procédé en vertu de la revendication n° 4, lorsque la base pyrimidique est la cytosine.
6. Le procédé en vertu de la revendication n° 4, lorsque la base pyrimidique est la 5-fluorocytosine.
7. Le procédé en vertu de l'une ou l'autre des revendications n° 1 à 3, lorsque l'acide de Lewis est le triflate de triméthylsilyle ou bien l'iodotriméthylsilane.
8. Le procédé en vertu de la revendication n° 3, lorsque l'auxiliaire chiral est le (*α*)-menthol ou bien le (*l*)-menthol.
9. Le procédé en vertu de l'une ou l'autre des revendications n° 1 à 3, lorsque R₃ est sélectionné parmi les groupes suivants : alkoxycarbonyle, carboxyles, diéthylcarboxamide, pyrrolidine amide, méthylcétone et phénylcétone.
10. Le procédé en vertu de la revendication n° 9, lorsque R₃ est un groupe alkoxycarbonyle ou bien carboxy.

11. Un intermédiaire de formule (II)



où

W représente O, S, S=O, SO₂, NZ ou CH₂;X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;Y représente O, S, CH₂, CH, CHF ou CHOH;

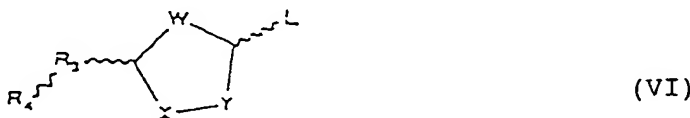
Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;

à condition que lorsque Y est CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂; et en plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;

R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S), substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine; et

L représente un groupe partant.

12. Un intermédiaire de formule (VI)



où

W représente O, S, S=O, SO₂, NZ ou CH₂;X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;Y représente O, S, CH₂, CH, CHF ou CHOH;

Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;

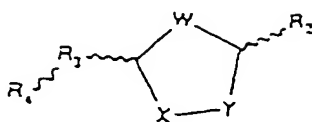
à condition que lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂; et de plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;

R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle, substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S) substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine;

R₄ représente un auxiliaire chiral; et

L représente un groupe partant.

13. Un intermédiaire de formule (VII)



(VII)

où

W représente O, S, S=O, SO₂, NZ ou CH₂;X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;Y représente O, S, CH₂, CH, CHF ou CHOH;

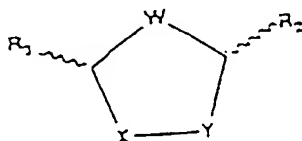
Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;

à condition que lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂;
et de plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;

R₂ est une base purique ou pyrimidique, ou un analogue ou un dérivé de cette base;

R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle, substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S), substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine; et R₄ représente un auxiliaire chiral.

14. Un intermédiaire de formule (VIII)



(VIII)

où

W représente O, S, S=O, SO₂, NZ ou CH₂;X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;Y représente O, S, CH₂, CH, CHF ou CHOH;

Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle; à condition que lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂;

R₂ est une base purique ou pyrimidique, ou un analogue ou un dérivé de cette base;

à condition que lorsque X est un groupe CH, Y soit également un groupe CH, et que lorsque X est un groupe CHN₃, R₂ ne soit ni l'adénine, ni un analogue ou un dérivé de l'adénine; et

R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle, substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S) substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine.

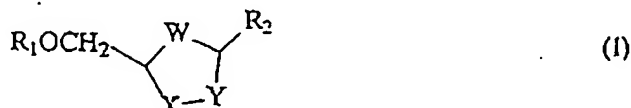
15. Un intermédiaire sélectionné parmi les composés suivants :

cis et *trans*-2R-carboéthoxy-5-hydroxytétrahydrofurane;*cis* et *trans*-2S-carboéthoxy-5-hydroxytétrahydrofurane;*cis* et *trans*-2R-carboéthoxy-5-acétoxytétrahydrofurane;

cis et *trans*-2S-carboéthoxy-5-acétoxytétrahydrofurane;
 1'S-(N-4-acétylcytosine-1-yl)-4'R-carboéthoxytétrahydrofurane;
 1'S-(cytosine-1-yl)-4'R-carboéthoxytétrahydrofurane;
 1'R-(5-fluorocytosine-1-yl)-4'S-carboéthoxytétrahydrofurane et 1'S-(5-fluorocytosine-1-yl)-4'S-carboéthoxy-
 tétrahydrofurane; et
 1'S-(5-fluorocytosine-1-yl)-4'R-carboéthoxytétrahydrofurane et 1'R-(5-fluorocytosine-1-yl)-4'R-carboéthoxy-
 tétrahydrofurane.

Revendications pour l'Etat contractant suivant : ES

1. Un procédé de synthèse diastéréosélective de *cis*-nucléosides optiquement actifs, d'analogues et de dérivés de nucléosides de formule (I) :



où

R₁ représente l'hydrogène ou un groupe acyle;

R₂ représente une base purique ou pyrimidique, ou un analogue ou un dérivé de cette base;

W représente S, S=O ou SO₂, O, NZ ou CH₂;

X représente O, S, S=O ou SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;

Y représente O, S, CH₂, CH, CHF ou CHOH; et

Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;

à condition que W ne soit ni O, ni S, ni S=O, ni SO₂, lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂; et,

en plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;

le procédé comprenant l'étape de glycosylation de la base purique ou pyrimidique, ou de l'analogue ou du dérivé de cette base, avec un seul énantiomère du composé de formule (II).



où

R₃ est l'un des groupes suivants : carbonyle substitué par l'hydrogène ou un groupe hydroxyle, trialkylsilyl, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyl substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyl (C=S) substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyl; homologues du thiocarbonyl et homologues de l'azométhine; et

L représente un groupe partant, utilisant un acide de Lewis de formule (III)

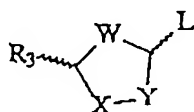


où

R₅, R₆ et R₇ sont choisis indépendamment parmi les groupes suivants : hydrogène; alkyle C₁₋₂₀ pouvant être substitué par un groupe fluoro, bromo, chloro, iodo, alkoxy C₁₋₆ ou aryloxy C₆₋₂₀; aralkyle C₇₋₂₀ pouvant être substitué par un halogène, un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; aryle C₆₋₂₀ pouvant être substitué par un groupe fluoro, bromo, chloro, iodo, alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; trialkylsilyle; fluoro; bromo; chloro et iodo; et

R₈ est sélectionné parmi les groupes suivants : fluoro; bromo; chloro; iodo; esters sulfonates C₁₋₂₀, pouvant être substitués par un groupe fluoro, bromo, chloro ou iodo; esters d'alkyle C₁₋₂₀, pouvant être substitués par un groupe fluoro, bromo, chloro ou iodo; halogénures polyvalents; silyles trisubstitués de formule générale (R₅)(R₆)(R₇)Si (où R₅, R₆ et R₇ ont été définis ci-dessus); aryle C₆₋₂₀ sélénényle saturé ou insaturé; arylsulfényle C₆₋₂₀ substitué ou non; alkoxyalkyle C₆₋₂₀ substitué ou non; et trialkysiloxy.

2. Le procédé en vertu de la revendication n° 1, comprenant de plus l'étape de réduction du groupe R₃ de la base purique ou pyrimidique glycosylée, ou de l'analogue ou du dérivé de cette base glycosylée, visant à produire le *cis*-nucléoside optiquement actif, ou l'analogue ou le dérivé de ce nucléoside de formule (I).
3. Le procédé en vertu de la revendication n° 1, comprenant de plus l'étape de résolution du composé de formule (II) en un seul énantiomère, par l'utilisation d'un auxiliaire chiral, préalablement à la glycosylation de la base purique ou pyrimidique.
4. Le procédé en vertu de l'une ou l'autre des revendications n° 1 à 3, lorsque R₂ est une base pyrimidique.
5. Le procédé en vertu de la revendication n° 4, lorsque la base pyrimidique est la cytosine.
6. Le procédé en vertu de la revendication n° 4, lorsque la base pyrimidique est la 5-fluorocytosine.
7. Le procédé en vertu de l'une ou l'autre des revendications n° 1 à 3, lorsque l'acide de Lewis est le triflate de triméthylsilyle ou bien l'iodotriméthylsilane.
8. Le procédé en vertu de la revendication n° 3, lorsque l'auxiliaire chiral est le (*α*)-menthol ou bien le (*l*)-menthol.
9. Le procédé en vertu de l'une ou l'autre des revendications n° 1 à 3, lorsque R₃ est sélectionné parmi les groupes suivants : alkoxy-carbonyle, carboxyles, diéthylcarboxamide, pyrrolidine amide, méthylcétone et phénylcétone.
10. Le procédé en vertu de la revendication n° 9, lorsque R₃ est un groupe alkoxy-carbonyle ou bien carboxy.
11. Un procédé de production d'un intermédiaire de formule (II)



(II)

où

- W représente O, S, S=O, SO₂, NZ ou CH₂;
 X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;
 Y représente O, S, CH₂, CH, CHF ou CHOH;
 Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;
 à condition que lorsque Y est CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂; et en plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;
 R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ dialkylamino C₁₋₁₀, ou en C par l'hydrogène ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀, thiocarbonyle (C=S), substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine; et
 L représente un groupe partant;

y compris l'étape de réduction chimiosélective d'un intermédiaire de formule (IV) :



10 et la conversion du groupe hydroxyle résultant en groupe partant L.

12. Un procédé de production d'un intermédiaire de formule (VI)



20 où

W représente O, S, S=O, SO₂, NZ ou CH₂;

X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;

Y représente O, S, CH₂, CH, CHF ou CHOH;

Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;

25 à condition que lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂; et de plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;

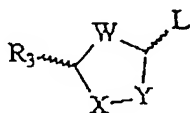
30 R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle, substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S) substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine;

R₄ représente un auxiliaire chiral; et

35 L représente un groupe partant;

y compris l'étape de couplage d'un intermédiaire de formule (II) avec un auxiliaire chiral :

(II)



13. Un procédé de production d'un intermédiaire de formule (VII)



55 où

W représente O, S, S=O, SO₂, NZ ou CH₂;

X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;

Y représente O, S, CH₂, CH, CHF ou CHOH;

Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;
à condition que lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂; et

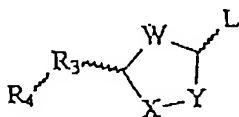
de plus, à condition que lorsque X est un groupe CH, Y soit également un groupe CH;

R₂ est une base purique ou pyrimidique, ou un analogue ou un dérivé de cette base;

R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle, substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S), substitué par in groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine; et

R₄ représente un auxiliaire chiral;

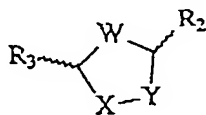
y compris l'étape de réaction entre un intermédiaire de formule (VI) et une base purique ou pyrimidique silylée, ou un analogue ou un dérivé de cette base, R₂;



(VI)

où L est un groupe partant.

14. Un procédé de production d'un intermédiaire de formule (VIII)



(VIII)

où

W représente O, S, S=O, SO₂, NZ ou CH₂; X représente O, S, S=O, SO₂, NZ, CH₂, CHF, CH, CHN₃ ou CHOH;
Y représente O, S, CH₂, CH, CHF ou CHOH;

Z représente l'hydrogène, ou un groupe hydroxyle, alkyle ou acyle;

à condition que lorsque Y est un groupe CH₂ et que X est O, S, S=O ou SO₂, W ne soit ni O, ni S, ni S=O, ni SO₂;

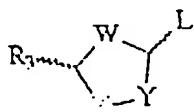
R₂ est une base purique ou pyrimidique, ou un analogue ou un dérivé de cette base;

à condition que lorsque X est un groupe CH, Y soit également un groupe CH, et que lorsque X est un groupe CHN₃, R₂ ne soit ni l'adénine, ni un analogue ou un dérivé de l'adénine; et

R₃ est sélectionné parmi les groupes suivants : carbonyle substitué par l'hydrogène, ou un groupe hydroxyle, trialkylsilyle, trialkylsiloxy, alkyle C₁₋₃₀, aralkyle C₇₋₃₀, alkoxy C₁₋₃₀, amine C₁₋₃₀ (primaire, secondaire ou tertiaire), thiol C₁₋₃₀, aryle C₆₋₂₀, alkényle C₁₋₂₀ ou alkynyle C₁₋₂₀; 1,2-dicarbonyle, substitué par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; anhydride substitué, par un groupe alkyle C₁₋₆ ou aryle C₆₋₂₀; azométhine substituée en N par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₁₀ ou dialkylamino C₁₋₁₀, ou en C par l'hydrogène, ou un groupe alkyle C₁₋₂₀ ou alkoxy C₁₋₂₀; thiocarbonyle (C=S) substitué par un groupe hydroxyle, alkoxy C₁₋₂₀ ou thiol C₁₋₂₀; homologues du carbonyle; homologues du thiocarbonyle et homologues de l'azométhine;

y compris l'étape de réaction entre un intermédiaire de formule (II) et une base purique ou pyrimidique silylée,

ou un analogue ou un dérivé de cette base, R₂ :



(II)

où L est un groupe partant.

15. Un procédé en vertu des revendications 11 ou 14, où l'intermédiaire produit est sélectionné parmi les composés suivants :

cis et *trans*-2R-carboéthoxy-5-hydroxytétrahydrofurane;
cis et *trans*-2S-carboéthoxy-5-hydroxytétrahydrofurane;
cis et *trans*-2R-carboéthoxy-5-acétoxytétrahydrofurane;
cis et *trans*-2S-carboéthoxy-5-acétoxytétrahydrofurane;
 1'S-(N-4-acétylcytosine-1-yl)-4'R-carboéthoxytétrahydrofurane;
 1'S-(cytosine-1-yl)-4'R-carboéthoxytétrahydrofurane;
 1'R-(5-fluorocytosine-1-yl)-4'S-carboéthoxytétrahydrofurane et
 1'S-(5-fluorocytosine-1-yl)-4'S-carboéthoxytétrahydrofurane; et
 1'S-(5-fluorocytosine-1-yl)-4'R-carboéthoxytétrahydrofurane et
 1'R-(5-fluorocytosine-1-yl)-4'R-carboéthoxytétrahydrofurane.